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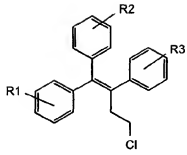
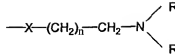
(54) **Title:** TRIPHENYLALKENE DERIVATIVES AND THEIR USE AS SELECTIVE ESTROGEN RECEPTOR MODULATORS



(I)



(II)

(57) **Abstract:** The invention provides novel selective estrogen receptor modulator compounds of general formula (I), wherein R1 and R2, which are the same or different are a) H, halogen, OCH_3, OH; or b) (II), where X is O, NH or S; and n is an integer from 1 to 4; and R4 and R5, which are the same or different, are a 1 to 4 carbon alkyl, H, $-CH_2C \equiv CH$ or $-CH_2CH_2OH$; or R4 and R5 form an N-containing five- or six-membered ring or heteroaromatic ring; or c) $-Y-(CH_2)_kCH_2-O-R6$, where Y is O, NH or S and n is an integer from 1 to 4; and R6 is H, $-CH_2CH_2OH$, or $-CH_2CH_2Cl$; or d) 2,3-dihydroxypropoxy, 2-methylsulfamylethoxy, 2-chloroethoxy, 1-ethyl-2-hydroxyethoxy, 2,2-diethyl-2-hydroxyethoxy or carboxymethoxy; and R3 is H, halogen, OH or $-OCH_3$; and their non-toxic pharmaceutically acceptable salts and esters and mixtures thereof, which compounds exhibit valuable pharmacological properties.

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TRIPHENYLALKENE DERIVATIVES AND THEIR USE AS SELECTIVE ESTROGEN RECEPTOR MODULATORS

FIELD OF INVENTION

This invention relates to triphenylalkene derivatives and their use as selective estrogen receptor modulators (SERMs).

BACKGROUND OF INVENTION

The publications and other materials used herein to illuminate the background of the invention, and in particular, cases to provide additional details respecting the practice are incorporated by reference.

Estrogens have been known as female sex hormones. However, lately many tissue-specific properties for estrogens have been described in organs, which are not classically considered to be estrogen-sensitive or estrogen-responsive. During the menopause the secretion of estrogens is dramatically decreased. Subsequently elderly women develop commonly climacteric symptoms including hot flushes, sweating, insomnia, depression, headache, vaginal dryness, cardiovascular symptoms, urinary incontinence, swelling feeling, breast tenderness and fatigue. In long-term estrogen deficiency induces cardiovascular disorders and osteoporosis which increase the risk of bone fractures and hospitalizations, which are very expensive to the society. Estrogens are increasingly used for the treatment of climacteric symptoms, but on the other hand estrogen use increases the risk of uterine and breast cancers (Lobo, 1995). Estrogens are shown to be beneficial also in the prevention of Alzheimer's disease (Henderson, 1997) and in the lowering of

LDL-cholesterol values and thus preventing cardiovascular diseases (Grodstein & Stampfer, 1998). New therapies which would have the benefits of estrogens, but not the carcinogenic risks are requested. Selective estrogen receptor modulators (SERMs) have been developed to fulfill these requirements (Macgregor & Jordan, 1998). However, the presently used SERMs have properties which are far from optimal. E.g. raloxifen use is limited by its strong antiestrogenic properties, which cause and worsen the climacteric symptoms, although the effects on the bone are beneficial (Khovidhunkit & Shoback, 1999). It would be most desirable to develop tissue-specific estrogens, which could be used in women in the treatment of climacteric symptoms, osteoporosis, Alzheimer's disease and/or cardiovascular diseases without the carcinogenic risk. At the best new SERMs could be given to men to protect against osteoporosis, cardiovascular diseases and Alzheimer's disease without estrogenic adverse events (gynecomastia, decreased libido etc.).

OBJECT AND SUMMARY OF THE INVENTION

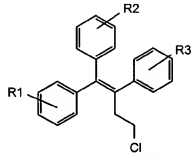
One object of the present invention is to provide novel selective estrogen receptor modulators.

Another object of the present invention is to provide a pharmaceutical composition comprising an amount effective to produce a tissue specific estrogenic and/or antiestrogenic effect of said novel selective estrogen receptor modulator compound or a non-toxic pharmaceutically acceptable salt thereof, and a pharmaceutically compatible acceptable carrier therefor.

An additional object of the present invention is to provide a method of producing a tissue specific estrogenic and/or antiestrogenic effect in a subject

in which such an effect is desired which comprises administering to said subject said novel selective estrogen receptor modulator compound, or a non toxic pharmaceutically acceptable salt thereof in an amount sufficient to produce the desired effect.

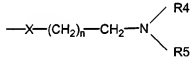
Thus, according to one aspect this invention concerns novel selective estrogen receptor modulator compounds of the general formula:



(I)

wherein R1 and R2, which are the same or different are

a) H, halogen, OCH_3, OH; or

b) 

where X is O, NH or S; and n is an integer from 1 to 4; and

R4 and R5, which are the same or different, are a 1 to 4 carbon alkyl, H, $-CH_2C{\equiv}CH$ or $-CH_2CH_2OH$; or

R4 and R5 form an N-containing five- or six-membered ring or heteroaromatic ring; or

c) $-Y-(CH_2)_nCH_2-O-R6$

where Y is O, NH or S and n is an integer from 1 to 4; and

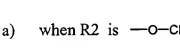
R6 is H, $-CH_2CH_2OH$, or $-CH_2CH_2Cl$; or

d) 2,3-dihydroxypropoxy, 2-methylsulfamylethoxy, 2-chloroethoxy, 1-ethyl-2-hydroxyethoxy, 2,2-diethyl-2-hydroxyethoxy or carboxymethoxy; and

R3 is H, halogen, OH or $-OCH_3$; and

their non-toxic pharmaceutically acceptable salts and esters and mixtures thereof,

provided that

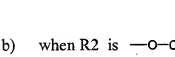
a) when R2 is  in the 4-position of the phenyl

where R4 and R5

i) are the same, either methyl or ethyl; or

ii) form an N-containing five-membered ring ;

then R1 and R3 cannot simultaneously be H; and

b) when R2 is  in the 4-position of the phenyl

where R4 and R5, which are the same or different, are methyl or H; or

when R2 is $-O-CH_2CH_2-OH$ or $-O-CH_2COOH$ in the 4-position of the phenyl,

then R1 and R3, cannot simultaneously be H, or OH in the 4-position of the phenyl; and

if R1 is OH in the 4-position of the phenyl, R3 cannot be H.

According to another aspect the invention concerns a pharmaceutical composition comprising an amount effective to produce a tissue specific

estrogenic and/or antiestrogenic effect of said novel selective estrogen receptor modulator compound or non-toxic pharmaceutically acceptable salt thereof, and a pharmaceutically compatible acceptable carrier therefor.

According to an additional aspect the invention concerns a method of producing a tissue specific estrogenic and/or antiestrogenic effect in a subject in which such an effect is desired which comprises administering to said subject said novel selective estrogen receptor modulator compound, or a non-toxic pharmaceutically acceptable salt thereof in an amount sufficient to produce the desired effect.

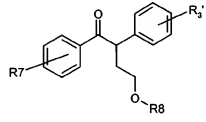
DETAILED DESCRIPTION OF THE INVENTION

This invention relates to the use of novel selective estrogen receptor modulators (SERMs) and their pharmaceutical preparations in men and women for the treatment of degenerative diseases and symptoms due to estrogen deficiency. Typically SERMs act as estrogens in bone and cardiovascular system while they are antiestrogenic in breast tissue. SERMs may have agonistic and antagonistic effects in other tissues also. Depending on their chemical structure and hormonal properties some compounds can be especially suited for elderly women for the prevention of osteoporosis whereas others (which are not feminizing estrogens) may also be used in men in the prevention of osteoporosis, cardiovascular diseases and Alzheimer's disease. Some compounds are specifically suited for the treatment of climacteric symptoms in menopausal women. It is the common property of the described novel compounds that they are antiestrogenic in the mammary gland and inhibit the proliferation of breast cancer cells. They are also weak

estrogens in the uterus and do not induce uterine cancers, the side effect of the well known SERM, tamoxifen.

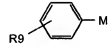
The new SERMs of the present invention thus have tissue-specific estrogenic and/or antiestrogenic effects in vitro and in vivo and are useful in the prevention and treatment of osteoporosis, cardiovascular diseases and Alzheimer's disease in men and women, as well as in the treatment of climacteric symptoms and breast cancer in women.

The compounds of formula (I) can be prepared by a process which comprises reaction of a compound of the formula



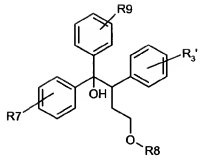
(II)

where R7 is the same as R1 or R2 as defined before or is a protected such group, R_3' is R3 as defined before or a protected OH, R8 is benzyl or tetrahydropyranyl, with an organometallic compound of the formula



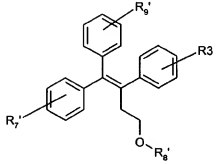
(III)

where R9 is H , R1 or R2 as defined before or is a protected such group and M is -Mg-halogen or Li, to give a compound of the formula



(IV)

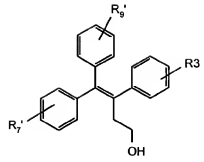
where R_3', R7, R8, and R9 are as defined above. R8 is tetrahydropyranyl when R7 or R9 is -X-$(CH_2)_nCH_2$-OR6 where X and n are as defined in (I). The compound (IV) is dehydrated by an appropriate acid catalyst preferable with acetic anhydride / acetyl chloride to give a triphenylethylene derivative of the formula



(V)

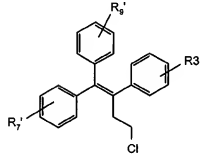
where R_8' is H or benzyl, R_7' and R_9' are R1 and R2 or benzyl protected OH or benzyl protected -XCH_2CH_2OR6. The possible protecting tetrahydropyranyl groups in R3, R7, R8 and R9 are removed in this process to give radicals R3, R_7', R_8' and R_9'.

The removal of the possible benzylic R_8' can be carried out by treatment with Zn and acetyl chloride in toluene to give the triphenylbutenol of the formula



(VI)

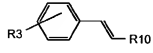
The hydroxy compound (VI) can be converted to a corresponding chloride by treatment with thionyl chloride or with triphenyl phosphine-carbon tetrachloride in organic solvent to give the compound of the formula



(VII)

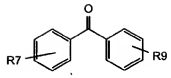
The claimed compounds (I) are prepared from the compounds of the formula (VII) where R_7' and/or R_9' are benzyl protected -XCH_2CH_2OR6 by treatment with Zn and acetyl chloride in organic solvent or by catalytic hydrogenation.

Another process to prepare compounds of the formula (IV) is the hydroalumination reaction of a "styrene" derivative of the formula



(VIII)

where R10 is -CHO, -CH_2OH, -COOH or a corresponding ester and R3 is as defined before with a benzophenone derivative of the formula



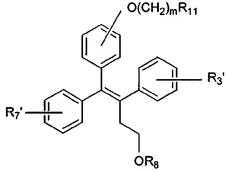
(IX)

Yet another process for the preparation of the compounds of the invention comprises O-alkylation of the compound of the formula (V) where R_7' and/or R_9' is OH with an alkyl halide derivative of the formula

R11-$(CH_2)_m$-halogen (X)

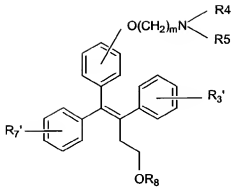
where m is an integer from 1 to 5 and R11 is halogen,  or -OR_6'

where R_6' is R6 or protected R6, or -COOR to give a compound of the formula



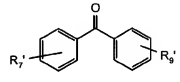
(XI)

The compound of the formula (XI) where R11 is halogen is reacted with an amine of the formula  to give a compound of the formula



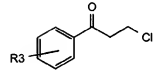
(XII)

Yet another process for the preparation of the compounds of the formula (VII) comprises the McMurry reaction of an benzophenone derivative of the formula



(XIII)

where R_7' and R_9' are as defined before, with an 3-chloropropiophenone derivative of the formula



(XIV)

where R3 is as defined before.

The claimed compound of the formula (I) where R1 or R2 is 2,2-diethyl-2-hydroxyethoxy can be prepared by reaction of the compound of the formula (XI), where m is 1 and R11 is -COOR, with ethylmagnesium bromide.

The claimed compound of the formula (I) where R1 or R2 is 1-ethyl-2-hydroxyethoxy can be prepared by O-alkylation of the compound of the

formula (V), where R_7' or R_9' is OH with ethyl α-bromobutyrate and by reduction of the formed ester by lithium aluminum hydride.

Experimental section

Methods

Evaluation of estrogenic and antiestrogenic properties of compounds in MCF-7 cell growth experiments in vitro

Estrogen-sensitive human breast cancer cells, MCF-7 (McGrath clone), were maintained in RPMI-1640 medium supplemented with 10 % fetal calf serum, 2 mM L-glutamine, 10 µg/ml insulin and 10 µg/ml gentamicin. The cells were grown as monolayer cultures in 75 cm^2 plastic tissue culture flask (Nunc, Roskilde, Denmark) in 25 ml medium at 37 °C in an atmosphere of 95 % air, 5 % CO_2 and subcultured twice a week.

For experiments involving hormone or anti-hormone treatment, the cells in exponential growth phase were precultivated in the absence of estradiol for one day. Cells were plated at a density of 3.5 x 10^3 cells/well in 96-well microtiter plates (Nunclon, Roskilde, Denmark) and incubated for 24 hours at 37 °C, 95 % air, 5 % CO_2, RPMI-1640 medium (L-glutamine and gentamicin as above) with 5 % stripped fetal calf serum (stripped twice with dextran-coated charcoal to remove the steroids) and without phenol red. After the incubation period the medium was removed. The exposure to study drugs was started immediately by adding fresh medium with 5 % stripped serum. Half of the cells were grown with estradiol, half without estradiol. Study compounds (dissolved in ethanol in 0.01 M concentration and diluted with the growth medium as appropriate) were added. The final concentrations of the

compounds were 1, 10, and 100 nM, and 1 and 10 μM. The cells were incubated for four days.

The amount of living cells was measured after 4 days by luminometer based on the amount of ATP and luciferase reaction as described by Kangas et al, 1984. This method allows evaluation of estrogenicity based on the ability of the compounds to stimulate the growth of the estrogen-dependent cells in the absence of estradiol. Estrogenicity was estimated by comparing the maximal growth stimulus (at any concentration) of study compound as per cent from growth stimulus by estradiol (100 % stimulus). In the present studies antagonism was estimated at the concentration of 1 μmol/l as per cent of theoretical full (100 %) antagonism, which would mean complete inhibition of estradiol-stimulus. At high concentrations molecules may also show toxicity. Toxicity was estimated as the fraction of dead cells (i.e. 100 % means that all cells have died during the exposure). The results are presented in Table 2.

Estimation of estrogenicity and antiestrogenicity in vivo

The classical method to evaluate estrogenic and antiestrogenic effect is immature mouse or rat uterus (Terenius, 1971). The animals were exposed for 3 days to the compounds to be investigated at the age of 18 days. On the fourth day the animals were asphyxicated with CO_2 and body weight and uterine weight was recorded. Estrogens increase the size and weight of the uterus (uterotropic effect) while antiestrogens inhibit this action. The compounds are therefore given alone and with estradiol in order to evaluate both agonistic and antagonistic effects. The results have been shown in Table 3 both as per cent of estrogen stimulation (100 %), and as inhibition of estrogen action (full inhibition is 100 %). The values are given at two dose levels, low i.e. 3–5 mg/kg and high i.e. 10–50 mg/kg. Estrogenic activity can be estimated also after a 4 weeks' treatment of ovariectomized rats based on the uterine size. This assay was carried out in selected molecules as shown in Table 4.

Estimation of effects to cholesterol and bone

Compounds were given p.o. to female rats for 4 or 5 weeks daily. At the end a blood sample was taken. Serum was separated by centrifugation and frozen until analyzed for total amount of cholesterol. Bone samples were taken from vertebra and tibia. Physical strength of the bones was studied as described by Peng et al, 1994. The assessments of the bone included:

Ash weight of tibial epiphyses

Epiphyses of one tibia was carefully prepared and burned. Samples were burned to remove water and organic material. Ash weight relates to the mineral content of the bone. In addition, bone samples were taken to study the histomorphometry. In some cases the bone formation was studied by injecting

tetracycline (50 mg/kg i.p. 10 days before autopsy) and calcein (20 mg/kg i.p. 3 days before autopsy). The method is based on permanent binding of tetracycline into growing bone and its detection by fluorescence (Peng et al, 1994).

Mechanical testing of bones

The mechanical testing of bones was carried out by materials testing machine, constructed in-house at Oulu University (Technical Services Department of the Medical Faculty). The testing machine is based on lever arm principle. One end of a steel lever is fixed. The pressing rod and the driving motor are connected to the lever arm with a moment ratio of 12.5 cm/50 cm = ¼. As a driving motor a linear actuator (SEY 10 Magnetic Elektromotoren AG, Switzerland) is used to obtain constant vertical movement (0.62 cm/s). The interchangeable compression head is mounted on the pressing rod for different tests transmitting compressive force to the specimen, and moving at a constant speed of 0.155 mm/s up to a maximal load capacity of 1200 N. The pressing rod is guided via an axial ball bearing to keep the movement vertical. Compressive force is measured by a temperature-compensated force sensor, which is attached to the stationary part of the compression stage. The measuring electronics include sensor calibration and adjustments.

Strength of femoral neck

The maximal load on the femoral neck was measured by the cantilever bending test. The supporter for the bone was a thick polymethyl methacrylate plate in which several holes of different sizes were drilled. On one side of each hole a groove was engraved for the third trochanter of the femur. The femur was cut exactly between the middle and lower third of the shaft. The bone was inserted perpendicularly and tightly into a suitable hole on the supporter. The lesser trochanter of each bone touched the surface of the plate.

This procedure allowed rapid and stable fixation of the bone without using any additional embedding materials. The concave compressing head, 2.5 mm in diameter, was made of aluminum. The femoral head-neck complex was tested until failure by loading the head with a force parallel to the shaft.

Estimation of antitumor activity in vivo

Antitumor activity was estimated by using DMBA (dimethylbenz[a]anthracene) model. One single peroral dose of DMBA (12 mg) initiates mammary gland carcinogenesis. New compounds were administered for 5 weeks when palpable tumors appeared. Size of the tumors and number of new tumors were carefully estimated once a week until termination. The model has been described in detail by Kangas et al, 1986. The growth of the tumors was measured once a week. All tumors were classified according to their growth properties to progressing, stable and regressing ones. Disappeared tumors were separately calculated. The tumors were considered to be progressing, if the tumor volume grew more than 8-fold during the 5 weeks dosing period, and regressing if the tumor volume decreased to one fourth or less from the volume in the beginning. If tumor volume changed less or remained unchanged, the tumors were considered to be stable.

Results

Altogether 46 compounds were evaluated by the methods described above which are included in the list of example compounds numbered and listed in Table 1.

TABLE 1 Reference numbers (No.) and names of example compounds.

No.	Compound
1	(E)-(2-{4-[4-Chloro-1-(4-fluorophenyl)-2-phenylbut-1-enyl]phenoxy}ethyl)-dimethylamine
2	(Z)-(2-{4-[4-Chloro-1-(4-fluorophenyl)-2-phenylbut-1-enyl]phenoxy}ethyl)-dimethylamine
3	(E)-(2-{4-[4-Chloro-1-(4-chlorophenyl)-2-phenylbut-1-enyl]phenoxy}ethyl)-dimethylamine
4	(E)-(2-{4-[4-Chloro-1,2-bis(4-chlorophenyl)but-1-enyl]phenoxy}ethyl)-dimethylamine
5	(Z)-(2-{4-[4-Chloro-1,2-bis(4-chlorophenyl)but-1-enyl]phenoxy}ethyl)-dimethylamine
6	(E)-4-Chloro-1-[4-(2-chloroethoxy)phenyl]-1,2-bis(4-chlorophenyl)-but-1-ene
7	(Z)-4-Chloro-1-[4-(2-chloroethoxy)phenyl]-1,2-bis(4-chlorophenyl)-but-1-ene
8	(E)-2-{4-[4-Chloro-2-phenyl-1-(4-fluorophenyl)but-1-enyl]phenoxy}ethanol
9	(E)-2-{4-[4-Chloro-1,2-bis(4-chlorophenyl)but-1-enyl]phenoxy}ethanol
10	(E)-3-{4-[4-Chloro-1-(4-chlorophenyl)-2-phenyl-but-1-enyl]phenoxy}-propane-1,2-diol
11	(Z)-4-Chloro-1-[4-(2-methylsulfanyl-ethoxy)phenyl]-1,2-diphenyl-but-1-ene
12	(E)-{4-[4-Chloro-1-(4-chlorophenyl)-2-phenylbut-1-enyl]phenoxy}acetic acid
13	(Z)-{4-[4-Chloro-1-(4-chlorophenyl)-2-phenylbut-1-enyl]phenoxy}acetic acid
14	(E)-1-(4-{2-[(2-Chloroethoxy]ethoxy}phenyl)-4-chloro-1-(4-chloro-phenyl)-2-phenyl-but-1-ene
15	(E)-1-(4-{2-[(2-Chloroethoxy]ethoxy}phenyl)-4-chloro-1-(4-fluorophenyl)-2-phenyl-but-1-ene
16	2-(4-{4-Chloro-1-[4-(2-hydroxyethoxy)phenyl]-2-phenyl-but-1-enyl}phenoxy)-1-ethanol
17	(E)-2-{4-[4-Chloro-2-phenyl-1-(4-chlorophenyl)but-1-enyl]phenoxy}ethanol
18	(Z)-2-[3-(4-Chloro-1,2-diphenyl-but-1-enyl)phenoxy]ethanol
19	(Z)-2-{2-[4-(4-Chloro-1,2-diphenylbut-1-enyl)phenoxy]ethoxy}ethanol
20	(Z)-3-[4-(4-Chloro-1,2-diphenyl-but-1-enyl)phenoxy]propane-1,2-diol

(Table 1 continued)

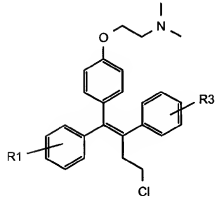
No.	Compound
21	(Z)-1-{2-[4-(4-Chloro-1,2-diphenyl-but-1-enyl)phenoxy]ethyl}-1H-imidazole
22	(Z)-2-({2-[4-(4-Chloro-1,2-diphenyl-but-1-enyl)phenoxy]ethyl}methylamino)ethanol
23	(Z)-(2-{4-[4-Chloro-2-(4-chlorophenyl)-1-phenylbut-1-enyl]phenoxy}ethyl)-dimethylamine
24	(E)-(2-{4-[4-Chloro-2-(4-chlorophenyl)-1-phenylbut-1-enyl]phenoxy}ethyl)-dimethylamine
25	(Z)-(2-{4-[4-Chloro-2-(4-fluorophenyl)-1-phenylbut-1-enyl]phenoxy}ethyl)-dimethylamine
26	(Z)-(2-{4-[4-Chloro-2-(4-chlorophenyl)-1-(4-methoxyphenyl)but-1-enyl]phenoxy}-ethyl)dimethylamine
27	(E)-(2-{4-[4-Chloro-2-(4-chlorophenyl)-1-(4-methoxyphenyl)but-1-enyl]phenoxy}-ethyl)dimethylamine
28	(Z)-1-(2-{4-[4-Chloro-2-(3-methoxyphenyl)-1-phenylbut-1-enyl]phenoxy}-ethyl)piperidine
29	(E)-1-(2-{4-[4-Chloro-2-(3-methoxyphenyl)-1-phenylbut-1-enyl]phenoxy}-ethyl)piperidine
30	(Z)-1-(2-{4-[4-Chloro-2-(2-methoxyphenyl)-1-phenylbut-1-enyl]phenoxy}-ethyl)piperidine
31	(E)-1-(2-{4-[4-Chloro-2-(2-methoxyphenyl)-1-phenylbut-1-enyl]phenoxy}-ethyl)piperidine
32	(Z)-1-[4-(2-Dimethylaminoethylsulfanyl)phenyl]-1,2-diphenyl-4-chloro-but-1-ene
33	(Z)-{2-[3-(4-Chloro-1,2-diphenylbut-1-enyl)phenoxy]ethyl}dimethylamine
34	(E)-3-{4-Chloro-1-[4-(2-hydroxyethoxy)phenyl]-2-phenyl-but-1-enyl}-phenol
35	(Z)-3-[4-(4-Chloro-1,2-diphenylbut-1-enyl)phenoxy]propan-1-ol
36	(Z)-2-[4-(4-Chloro-1,2-diphenyl-but-1-enyl)-phenylsulfanyl]ethanol
37	(Z)-2-{4-[4-Chloro-2-(4-chlorophenyl)-1-(4-methoxyphenyl)but-1-enyl]-phenoxy}ethanol
38	(Z)-1-(2-{4-[4-Chloro-2-(2-chlorophenyl)-1-phenylbut-1-enyl]phenoxy}-ethyl)piperidine
39	(E)-3-{4-Chloro-1-[4-(2-imidazol-1-yl-ethoxy)phenyl]-2-phenyl-but-1-enyl}-phenol
40	(Z)-3-{4-Chloro-1-[4-(2-imidazol-1-yl-ethoxy)phenyl]-2-phenyl-but-1-enyl}-phenol

(Table 1 continued)

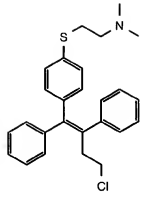
No.	Compound
41	(Z)-2-[4-(4-Chloro-1,2-diphenyl-but-1-enyl)phenylamino]ethanol
42	(Z)-4-{1-(2-Chloroethyl)-2-[4-(2-hydroxyethoxy)phenyl]-2-phenylvinyl}phenol
43	(E)-4-{1-(2-Chloroethyl)-2-[4-(2-hydroxyethoxy)phenyl]-2-phenylvinyl}phenol
44	(Z)-{2-[4-(4-Chloro-1,2-diphenylbut-1-enyl)phenoxy]ethyl}-methylprop-2-ynylamine
45	(Z)-3-[4-(4-Chloro-1,2-diphenylbut-1-enyl)phenoxymethyl]pentan-3-ol
46	(Z)-2-[4-(4-Chloro-1,2-diphenylbut-1-enyl)phenoxy]butan-1-ol
47	N-[4-(4-chloro-1,2-diphenylbut-1-enyl)phenyl]-N',N'-dimethyl-ethane-1,2-diamine

The structures of the example compounds are summarized as follows:

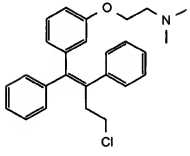
Compounds with a dimethylaminoethoxy tail



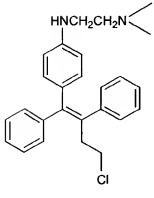
R1	R3	No.
4–F	H	1 and 2
4–Cl	H	3
4–Cl	4–Cl	4 and 5
H	4–Cl	23 and 24
H	4–F	25
4–OCH_3	4–Cl	26 and 27



No. 32

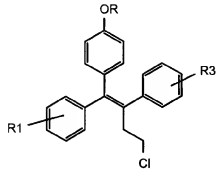


No. 33



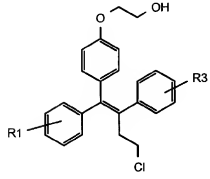
No. 47

Compounds with a dimethylaminoethoxy tail

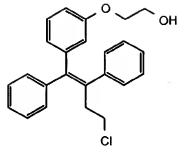


R1	R3	R	No.
H	H	CH_2CH_2imidazolyl	21
H	H	$CH_2CH_2N(CH_3)CH_2CH_2OH$	22
H	3-OCH_3	CH_2CH_2piperidinyl	28 and 29
H	4-OCH_3	CH_2CH_2piperidinyl	30 and 31
H	2–Cl	CH_2CH_2piperidinyl	38
3–OH	H	CH_2CH_2imidazolyl	39 and 40
H	H	$CH_2CH_2N(CH_3)CH_2C{\equiv}CH$	44

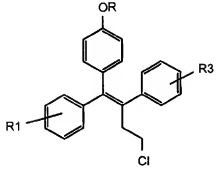
Alcohols



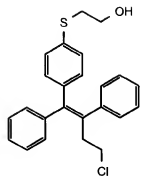
R1	R3	No.
4–F	H	8
4–Cl	4–Cl	9
4–OCH_2CH_2OH	H	16
4–Cl	H	17
3–OH	H	34
4–OCH_3	4–Cl	37
H	4–OH	42 and 43



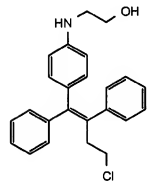
No. 18



R1	R3	R	No.
4–Cl	4–Cl	CH_2CH_2Cl	6 and 7
4–Cl	H	$CH_2CH(OH)CH_2OH$	10
H	H	$CH_2CH_2SCH_3$	11
4–Cl	H	CH_2CHOOH	12 and 13
4–Cl	H	$CH_2CH_2OCH_2CH_2Cl$	14
4-F	H	$CH_2CH_2OCH_2CH_2Cl$	15
H	H	$CH_2CH_2OCH_2CH_2OH$	19
H	H	$CH_2CH(OH)CH_2OH$	20
H	H	$CH_2CH_2CH_2OH$	35
H	H	$CHC(OH)(CH_2CH_3)_2$	45
H	H	$CH(CH_2CH_3)CH_2OH$	46



No. 36



No. 41

The estrogenic and antiestrogenic as well as cytotoxic effects of several compounds in vitro are presented in Table 2. It can be seen that the spectrum of hormonal activity of the compounds varies and thus gives the possibility to use the compounds in different clinical conditions.

Compounds with weak hormonal activity, which kill MCF-7 cells (human breast cancer cells) effectively at the highest investigated concentration (10 μM) could be used preferably in the treatment of breast cancer. Such compounds are among others compounds No. 1, 3, 16, 19, 26, 27, 39 and 40 (Table 2). These compounds and several others are less effective estrogens and antiestrogens than the well known breast cancer drugs tamoxifen and toremifene (Table 3). Especially compound No. 19 is of interest, because it is

a more effective anticancer drug in vivo in the DMBA-induced rat mammary tumor model even at very low doses than clinically used tamoxifen and toremifene (Table 6).

Compounds with weak estrogenic and no antiestrogenic action could be especially suitable for the prevention and treatment of osteoporosis and climacteric symptoms. Such compounds are (among others) compounds No. 3, 10, 11, 18, 19, 20, 25, 32, 36 and 44 (Tables 2, 3 and 4).

Compounds, which decrease cholesterol could be useful as cardiovascular drugs. For women some estrogenicity for such compounds can be allowed, but compounds which are not estrogens or are very weak estrogens and decrease cholesterol, could be used also in men for the prevention and treatment of cardiovascular diseases. Such compounds include (among others) compounds No. 3, 19, 20 (also for men) and 33 (for women) (Table 4). The same compounds are expected to be useful also in the treatment or prevention of Alzheimer's disease. In the latter case the cytotoxic action of the compounds should be weak, like e.g. with compound No. 33 (Table 2). It should be noted that compound No. 19 does not show any estrogenic action on the weight of the prostate gland at doses which are active in DMBA-induced mammary tumor model (Tables 6 and 7). Therefore it could be of special benefit in men and could be of benefit in addition to the above mentioned conditions in the treatment of prostate cancer.

The hormonal profile of the compounds may be in some cases different in vitro and in vivo, e.g. compound No. 1 has no estrogenic action in vitro (Table 2), but is a weak estrogen in vivo (Table 3). Therefore the examples above should be understood as examples of the usefulness in different

conditions. They should not be understood as limitations for their possible use in different clinical indications.

TABLE 2 Estrogenic, antiestrogenic, and cytotoxic effects of study compounds in MCF-7 cells. The details of estimations are given in the text. Maximal estrogenic agonism in the absence of estradiol was calculated in per cent of estradiol-stimulus (100 %). Antiestrogenic property was evaluated at the concentration of 1 μmol/l considering theoretical full antagonism as 100 per cent. Toxicity at the concentration of 10 μmol/l was evaluated as a fraction of dead cells when compared to the control (i.e. 100 means that all cells are dead). Known antiestrogens were used as references.

Compound	**Without estradiol (E2)**		**With estradiol (E2)**	
No.	Maximal Agonism (% of E2)	Maximal Cell Kill (% fraction of dead cells)	Antagonism at 1 μM (% of full antagonism)	Maximal Cell Kill (% fraction of dead cells)
1	1	100	8	100
2	100	32	29	100
3	1	100	1	94
4	10	90	10	100
5	11	100	31	100
6	0	47	16	40
8	31	2	92	52
9	14	45	9	62
10	34	7	0	35
11	14	26	0	55
14	12	10	27	57
15	74	82	5	9
16	22	90	23	96
17	0	44	17	38
18	30	10	1	40
19	14	14	21	50
20	8	5	25	60
21	5	80	0	91
22	1	15	12	41
23	14	89	5	93
24	46	89	4	98

TABLE 2 (continued)

Compound	Without estradiol (E2)		With estradiol (E2)	
No.	Maximal Agonism (% of E2)	Maximal Cell Kill (% fraction of dead cells)	Antagonism at 1 μM (% of full antagonism)	Maximal Cell Kill (% fraction of dead cells)
25	17	42	6	27
26	0	97	11	98
27	0	99	5	100
28	3	86	18	92
30	5	91	4	92
32	11	86	0	90
33	20	0	58	80
34	0	0	0	0
35	45	50	14	50
36	8	17	13	37
37	4	39	0	41
38	0	99	68	100
39	0	68	17	78
40	0	63	3	46
41	54	0	10	47
42	9	23	13	54
43	78	80	6	22
44	24	78	8	95
45	15	6	3	19
46	18	15	23	51
Tamoxifen	31	100	43	100
Toremifene	37	100	44	100
FC-1271a	23	50	21	80
ICI 164,384	9	100	100	100

TABLE 3 Uterotropic (e.g. estrogenic) and estrogen antagonistic effect of study compounds in the 3 day uterotropic assay in immature female rats. Estrogenic effect is estimated as per cent of maximal, estrogen-induced, action. Antiestrogenic effect is presented as per cent of theoretical complete inhibition of estrogen action (100 %).

Compound No.	Uterotropic effect (% of estradiol) Given without estradiol		Estrogen antagonism (% inhibition of estradiol) Given with estradiol	
dose:	3–5 mg/kg	10–50 mg/kg	3–5 mg/kg	10–50 mg/kg
1	42	74	26	31
3	44	54	65	38
19	13	37	10	44
20	33	62	5	20
20	48	72	26	39
21	26	39	10	20
35	43	66	35	32
36	14	29	0	5
38	73	72	0	12
39	9	19	50	70
40	13	9	45	54
44	55	75	n.d.	42
45	43	62	30	30
46	77	100	0	0
Tamoxifen	44	51	51	58
Toremifen	26	44	45	58
Raloxifene	11	13	90	92

TABLE 3 (continued)

Size of the uterus after a 4 weeks treatment of ovariectomized rats with the new compounds (peroral daily doses indicated in mg/kg). Sham-operated, estradiol treated and raloxifene treated ovariectomized rats served as controls.

Group	Uterine size (g)
Sham control	0.497 ± 0.103
Ovariectomized	0.099 ± 0.016
No. 3 3.0 mg/kg	0.140 ± 0.006
No. 19 1.0 mg/kg	0.192 ± 0.029
No. 19 5.0 mg/kg	0.221 ± 0.023
No. 20 1.0 mg/kg	0.133 ± 0.032
Raloxifene 3.0 mg/kg	0.141 ± 0.021
FC-1271a 5 mg/kg	0.411±0.042

TABLE 4 Effect of compound No. 3, 19 and 20 on rat serum cholesterol level in ovariectomized (OVX) rats after 4 weeks dosing. Estradiol was given to one group for comparison. The result indicates that ovariectomy causes increase of cholesterol level. Estradiol, compound No. 3, 19 and 20 can prevent this increase even at very low dose and decrease the level below the sham operated level. Number of animals was 8 in each group.

Group	Cholesterol level (mmol/l) in serum
Sham operated rat	3.8 ± 0.4
OVX rat	4.6 ± 0.7
OVX rat + estradiol 3 μg/kg	4.0 ± 0.4
OVX + No. 3 3 mg/kg	3.1 ± 0.4
OVX + No. 19 0.3 mg/kg	3.6 ± 0.4
OVX + No. 19 10 mg/kg	3.9 ± 0.6
OVX + No. 20 1 mg/kg	3.3 ± 0.6
OVX + No. 20 5 mg/kg	2.3 ± 0.4

TABLE 5 Effect of compounds No. 3, 19 and 20 on bone in ovariectomized rats after 4 weeks dosing. Rats were ovariectomized (controls sham operated). Compounds were given for 4 weeks at indicated doses (mg/kg) p.o. beginning one week after the ovariectomy. Tibial epiphyses and femoral neck were prepared for the estimation of the quality of the bone.

Group and dose (mg/kg)			Ash weight (mg) of tibial epiphyses	Maximal load (N) of femoral neck
Sham control		(n=10)	34.0 ± 2.9	86.7 ± 10.4*
OVX		(n=10)	32.2 ± 2.8	68.4 ± 8.5
No. 3	3.0 mg/kg	(n=22)	36.0 ± 3.4*	92.5 ± 11.1*
No. 19	1.0 mg/kg	(n=10)	34.8 ± 1.3*	81.6 ± 7.9*
No. 19	5.0 mg/kg	(n=10)	34.9 ± 1.9*	85.7 ± 17.0*
No. 20	3.0 mg/kg	(n=20)	35.0 ± 3.2	81.7 ± 15.2*
Raloxifene	3.0 mg/kg	(n=10)	34.9 ± 3.5	84.2 ± 18.4*

* indicates statistically significant ($p < 0.05$) difference to ovariectomized animals

TABLE 6 Antitumor effect of compound No. 19 on DMBA-induced rat mammary gland cancer. Compound No. 19 was given p.o. daily for 5 weeks at the indicated doses. Tumors were classified to growing, stable, regressing and disappeared as described in the text. Number of tumors in each group was counted and calculated as per cent of total tumor number. Number of animals in each group was 7. Compound No. 19 did not influence on the body weight of the animals when compared to controls.

Group		Growing	Stable	Regressing	Disappeared
Control		82 %	18 %	0 %	0 %
No. 19	3 mg/kg	20 %	20 %	40 %	20 %
No. 19	15 mg/kg	14 %	14 %	57 %	14 %
Tamoxifene	3 mg/kg	36 %	56 %	8 %	0 %
Toremifene	3 mg/kg	31 %	51 %	11 %	10 %

TABLE 7: Effect of compound No. 19 on the weight of the prostate gland in intact and castrated male rats after 4 weeks daily treatment with two different doses. Castration decreases markedly the prostate weight and estrogens are known to do the same. Compound No. 19 has no estrogenic effect at the dose of 0.5 mg/kg and is weakly estrogenic at the dose of 5.0 mg/kg. Note that this compound has significant antitumor action in the DMBA-induced mammary cancer model at 0.5 mg/kg dosage (Table 6).

Group	Weight of the prostate gland (mg) mean and sd
Control	2.60 ± 0,77
Castrated rats	0.59 ± 0,07
No. 19 0.5 mg/kg	2.66 ± 0,21
No. 19 5.0 mg/kg	1.58 ± 0,50
No. 19 0.5 mg/kg to castrated rats	0.59 ± 0,07
No. 19 5.0 mg/kg to castrated rats	0.62 ± 0,07

For the purpose of this invention, the novel SERMs or their pharmaceutically acceptable salts can be administered by various routes. The suitable administration forms include, for example, oral formulations, parenteral injections including intravenous, intramuscular, intradermal and subcutaneous injections; and transdermal or rectal formulations. Suitable oral formulations include e.g. conventional or slow-release tablets and gelatin capsules.

The required dosing of the novel SERMs will vary with the particular condition being treated, the severity of the condition, the duration of the treatment, administration route and specific compounds being employed. Typically the daily dose for an adult person is 5–200 mg, preferably 20–100 mg. SERMs can be given as tablets or other formulations like gelatin capsules alone or mixed in any clinically acceptable non-active ingredients which are used in the pharmaceutical industry.

EXAMPLES

Example 1

a) O-alkylation of 4-hydroxybenzophenone derivatives

In phase transfer catalysis (PTC) conditions

[4-(2-Dimethylaminoethoxy)phenyl]-(4-fluorophenyl)methanone

4-Hydroxybenzophenone (28.1 g, 0.13 mol) is dissolved in toluene (140 ml). Tetrabutylammonium bromide (TBABr) (2.1 g) is added. Aqueous 48 % sodium hydroxide (140 ml) is added at 50–55 °C. The mixture is heated to 80 °C and 2-chloroethyldimethylamine hydrochloride (total 20.0 g, 0.14 mol) is added in small portions and the reaction mixture is stirred at 97–100 °C for 3 h. The layers are separated and the organic layer is washed with water, dried over sodium sulfate and evaporated to dryness. Yield 33.0 g, 88 %. The product is used for the next step without further purification.

^{1}H NMR ($CDCl_3$): 2.36 (s, 6H), 2.77 (t, 2H), 4.15 (t, 2H), 6.99 (d, 2H), 7.15 (t, 2H), 7.27–7.83 (m, 4H)

Using the same method the following compounds are prepared:

(4-Clorophenyl)-[4-(2-dimethylaminoethoxy)phenyl]methanone

^{1}H NMR ($CDCl_3$): 2.36 (s, 6H), 2.77 (t, 2H), 4.15 (t, 2H), 6.98 (d, 2H), 7.45 (2H), 7.71 (d, 2H), 7.79 (d, 2H)

[4-(2-Benzyloxyethoxy)phenyl]-(4-fluorophenyl)methanone

^{1}H NMR ($CDCl_3$): 3.87 (dist.t, 2H), 4.24 (dist.t, 2H), 4.65 (s, 2H), 6.99 (d, 2H), 7.15 (t, 2H), 7.32-7.39 (m, 5H), 7.76–7.83 (m, 4H)

[4-(2-Benzyloxyethoxy)phenyl]-(4-chlorophenyl)methanone

^{1}H NMR ($CDCl_3$): 3.86 (t, 2H), 4.24 (t, 2H), 4.65 (s, 2H), 6.99 (d, 2H), 7.3-7.4 (m, 5H), 7.45 (d, 2H), 7.70 (d, 2H), 7.78 (d, 2H)

By acid catalysis

(4-Chlorophenyl)-[4-(tetrahydropyranyloxy)phenyl]methanone

4-Chloro-4'-hydroxybenzophenone (50 g, 0.215 mol) is dissolved in dichloromethane (400 ml). 3,4-Dihydro-2H-pyran (21.7 g, 0.257 mol) and a catalytic amount of p-toluenesulfonic acid are added to the solution. The solution is stirred for 6 hours at room temperature and then allowed to stand over night. 1 N aqueous sodium hydroxide solution (100 ml) is added to the reaction mixture and stirred for 15 minutes. Organic layer is separated and washed twice with 1 N aqueous sodium hydroxide solution and once with water. Dichloromethane solution is dried and evaporated to dryness. Yield 68.6 g.

^{1}H NMR ($CDCl_3$): 1.52–2.20 (m, 6H), 3.60-3.67 (m, 1H), 3.8–3.94 (m, 1H), 5.5–5.6 (m, 1H), 7.10 (d, 2H), 7.45 (d, 2H), 7.72 (d, 2H), 7.78 (d, 2H)

Using the same method the following compound is prepared:

Bis[4-(tetrahydropyranyloxy)phenyl]methanone

^{1}H NMR ($CDCl_3$): 1.55–2.20 (m, 12H), 3.6–3.7 (m, 2H), 3.8–4.0 (m, 2H), 5.5–5.6 (m, 2H), 7.11 (d, 4H), 7.78 (d, 4H)

NaH as a base

(4-Chlorophenyl)-[4-(2,2-dimethyl-[1,3]dioxolan-4-ylmethoxy)-phenyl]-methanone

Sodium hydride (3.4 g, 0.072 mol) in oil is washed with heptane and mixed with dimethyl formamide (DMF) (120 ml). 4-Chloro-4'-hydroxybenzophenone (12 g, 0.052 mol) in DMF is added dropwise to the solution and the reaction mixture is stirred for an hour at room temperature. Then toluene-4-sulfonic acid 2,2-dimethyl-[1,3]dioxolan-4-yl methyl ester (17.7 g, 0.0618 mol, prepared from S-1,2-O-isopropyl glycerol and p-toluenesulfonyl chloride) in DMF is added dropwise to the solution during an hour. The mixture is heated to 60 °C and stirred at that temperature for two days. 1 N aqueous sodium hydroxide solution (200 ml) is added to reaction mixture and the solution is extracted three times with toluene (60 ml). Toluene layers are combined and washed twice with water (60 ml), dried and evaporated to dryness. The residue is crystallized from methanol. Yield 13.7 g, 76.7 %.

^{1}H NMR ($CDCl_3$): 1.42 (s, 3H), 1.48 (s, 3H), 3.90–4.24 (m, 4H), 4.52 (quintet, 1H), 6.99 (d, 2H), 7.46 (d, 2H), 7.71 (d, 2H), 7.79 (d, 2H)

b) Hydroalumination reaction of benzophenone derivatives with cinnamaldehyde or a methyl cinnamate

1-[4-(2-N,N-dimethylaminoethoxy)phenyl]-1-(4-fluorophenyl)-2-phenylbutane-1,4-diol

Lithium aluminum hydride (2.6 g, 0.068 mol) is added into dry tetrahydrofuran (120 ml) under nitrogen atmosphere. Cinnamaldehyde (13.8 g, 0.1 mol) in dry tetrahydrofuran (30 ml) is added at 24–28 °C. The reaction

mixture is stirred at ambient temperature for 1 h. [4-(2-Dimethylamino-ethoxy)phenyl]-(4-fluorophenyl)- methanone (29.6 g, 0.103 mol) in dry tetrahydrofuran (60 ml) is added at 50–55 °C. The reaction mixture is stirred at 60 °C for 3 h. Most of tetrahydrofuran is evaporated. Toluene (300 ml), 48 % aqueous sodium hydroxide (118 ml) and water (30 ml) are added. The mixture is refluxed for 10 min and the aqueous layer is separated while warm. The NaOH treatment is repeated. The toluene layer is washed twice with hot water. The product is crystallized from toluene as a mixture of stereoisomers (26.4 g, 62 %).

^{1}H NMR ($CDCl_3$ + MeOH-d4): 1.95–2.12 (m, 2H), 2.30 and 2.37 (2s, together 6H), 2.68 and 2.77 (2t, together 2H), 3.31–3.48 (m, 2H) under which the signal of $\underline{CH}CH_2$ of the other diastereoisomer, 3.80 (dd, $\underline{CH}CH_2$ the other diastereoisomer), 3.95 and 4.08 (2t, together 2H), 6.62 and 6.91 (2d, together 2H), 7.03 and 6.72 (2t, together 2H), 7.05–7.20 (m, 7H), 7.51 (m, 2H)

Using the same method the following compounds are prepared:

1-(4-Chlorophenyl)-1-[4-(2-N,N-dimethylaminoethoxy)phenyl]-2-phenyl-butane 1,4-diol , mixture of stereoisomers.

^{1}H NMR ($CDCl_3$ + MeOH-d4): 1.85–2.10 (m, 2H), 2.27 and 2.33 (2s, together 6H), 2.66 and 2.75 (2t, together 2H), 3.25–3.50 (m, 2H), 3.62 and 3.84 (t and dd, together 1H), 3.93 and 4.04 (2t, together 2H), 6.6–7.6 (13H)

1-[4-(2-Benzyloxyethoxy)phenyl]-1-(4-fluorophenyl)-2-phenylbutane-1,4-diol, mixture of stereoisomers.

^{1}H NMR ($CDCl_3$): 1.92–2.15 (m, 2H), 3.30–3.48 and 3.48–3.66 (2m, together 2H), 3.74 and 3.83 (2 dist.t, together 2H), 4.02 and 4.15 (2 dist.t, together 2H), under the two last signal groups $CHCH_2$, 4.58 and 4.63 (2s, together 2H), 6.6-7.6 (18H)

1-[4-(2-Benzyloxyethoxy)phenyl]-1,2-bis(4-chlorophenyl)butane-1,4-diol, mixture of stereoisomers.

4-Chlorocinnamic acid methyl ester is used instead of cinnamaldehyde.

^{1}H NMR ($CDCl_3$): 1.80–2.15 (m, 2H), 3.2–3.4 and 3.4–3.6 (2m, together 2H), 3.75 and 3.82 (2 t, together 2H), 3.95 (dist.t, 1H) , 4.00 and 4.14 (2 t, together 2H), 4.59 and 4.63 (2s, together 2H), 6.80–7.55 (17 H)

1,2-Bis(4-chlorophenyl)-1-[4-(2-dimethylaminoethoxy)phenyl]butane-1,4-diol, mixture of stereoisomers.

4-Chlorocinnamic acid methyl ester is used instead of cinnamaldehyde.

^{1}H NMR ($CDCl_3$ + MeOH-d_4): 1.85–2.20 (m, 2H), 2.35 and 2.37 (2s, together 6H), 2.77 and 2.82 (2t, together 2H), 3.20-3.45 (m, together 2H), 3.81 and 3.85 (2 dist. t, together 1H), 4.10 and 4.21 (2 t, together 2H), 6.9–7.8 (m, 12 H)

1,1-Bis[4-(tetrahydropyranyloxy)phenyl]-2-phenylbutane-1,4-diol

^{1}H NMR ($CDCl_3$): 1.5–2.1 (m, 14 H), 3.3–4.1 (m, 7H), 5.25-5.28 (m, 1H), 6.77 (d, 2H), 7.00 (d, 2H), 7.1–7.2 (m, 9H), 7.47 (d, 2H)

1-(4-Chlorophenyl)-2-phenyl-1-[4-(tetrahydropyranyloxy)phenyl]-butane-1,4-diol

^{1}H NMR ($CDCl_3$): 1.5–2.1 (m, 8H), 3.2–4.0 (m, 5H), 5.27 (m, 1H), 6.79 (d, 2 H), 6.9–7.32 (m, 9H), 7.5 (d, 2H)

1-(4-Chlorophenyl))-[4-(2,2-dimethyl-[1,3]dioxolan-4-ylmethoxy)-phenyl]-2-phenylbutane-1,4-diol

^{1}H NMR ($CDCl_3$): 1.37 and 1.40 and 1.42 and 1.46 (4s, together 6H), 1.9–2.1 (m, 2H), 3.2-4.5 (m, 8H), 6.6–7.55 (m, 13H)

1,2-Diphenyl-1-[3-(tetrahydropyranyloxy)phenyl]-butane-1,4-diol

is prepared starting from phenyl-[3-(tetrahydropyranyloxy)phenyl]methanone and cinnamaldehyde. The compound is used in the next reaction step without further purification.

c) Dehydration of 1,1,2-triarylbutane-1,4-diol derivatives

4-[4-(2-Dimethylaminoethoxy)phenyl]-4-(4-fluorophenyl)-3-phenylbut-3-en-1-ol

1-[4-(2-N,N-Dimethylaminoethoxy)phenyl]-1-(4-fluorophenyl)-2-phenyl-butane-1,4-diol (8.46 g, 0.02 mol) is refluxed in 80 ml of acetic anhydride for 3 h. The mixture is cooled to 60 °C and acetyl chloride (7.85 g, 0.1 mol) is added. The mixture is stirred at 80–90 °C for 4 h. The solvents are evaporated. Solution containing 5 % of sodium hydroxide in 80 % aqueous methanol is added and the mixture is stirred for 2 h at RT. Methanol is evaporated. Water is added and the product is extracted into ethyl acetate. The organic layer is washed with water, dried and evaporated. The residue (9.5 g)

is mixture of E- and Z-isomers of the product. The isomers are separated by flash chromatography (eluent: toluene:triethylamine 9:1).

E-isomer, ^{1}H NMR ($CDCl_3$): 2.27 (s, 6H), 2.64 (t, 2H), 2.74 (t, 2H), 3.57 (t, 2H), 3.92 (t, 2H), 6.57 (d, 2H), 6.75 (d, 2H), 7.03 (t, 2H), 7.10–7.18 (m, 5H), 7.27 (dd, 2H)

Z-isomer, ^{1}H NMR ($CDCl_3$): 2.34 (s, 6H), 2.74 (t, 2H), 2,79 (t, 2H), 3.60 (t, 2H), 4.05 (t, 2H), 6.69 (t, 2H), 6.84 (dd, 2H), 6.91 (d, 2H), 7.09–7.17 (m, 5H), 7.20 (d, 2H)

Using the same method the following compounds are prepared:

4-(4-Chlorophenyl)-4-[4-(2-dimethylaminoethoxy)phenyl]-3-phenylbut-3-en-1-ol

E-isomer, ^{1}H NMR ($CDCl_3$): 2.27 (s, 6H), 2.64 (t, 2H), 2.73 (t, 2H), 3.56 (t, 2H), 3.91 (t, 2H), 6.56 (d, 2H), 6.74 (d, 2H), 7.10–7.34 (m, 9H)

4-[4-(2-Benzyloxyethoxy)phenyl]-4-(4-fluorophenyl)-3-phenylbut-3-en-1-ol

E-isomer, ^{1}H NMR ($CDCl_3$): 2.74 (t, 2H), 3.57 (m, 2H), 3.74 (dist.t, 2H), 4.01 (dist.t, 2H), 4.58 (s, 2H), 6.57 (d, 2H), 6.75 (d, 2H), 7.00–7.40 (m, 14H) from which the signal 7.03 (t, 2H) can be identified.

Z-isomer, ^{1}H NMR ($CDCl_3$): 2.79 (t, 2H), 3.60 (m, 2H), 3.84 (dist.t, 2H), 4.17 (dist.t, 2H), 4.65 (s, 2H), 6.69 (t, 2H), 6.83 (dd, 2H), 6.91 (d, 2H), 7.00–7.45 (m, 14H) from which the signal 7.20 (d, 2H) can be identified.

4-[4-(2-Benzyloxyethoxy)phenyl]-3,4-bis(4-chlorophenyl)-but-3-en-1-ol

E-isomer, ^{1}H NMR ($CDCl_3$): 2.70 (t, 2H), 3.50-3.65 (m, 2H), 3.75 (dist.t, 2H), 4.03 (dist.t, 2H), 4.59 (s, 2H), 6.59 (d, 2H), 6.73 (d, 2H), 7.00–7.40 (m, 13H)

3,4-Bis(4-chlorophenyl)-4-[4-(2-hydroxyethoxy)phenyl]but-3-en-1-ol

is produced as a sideproduct in the dehydration reaction of 1-[4-(2-benzyl-oxyethoxy)phenyl]-1,2-bis(4-chlorophenyl)butane-1,4-diol.

E-isomer, ^{1}H NMR ($CDCl_3$): 2.72 (t, 2H), 3.50-3.65 (m, 2H), 3.80–3.96 (m, 4H), 6.59 (d, 2H), 6.75 (d, 2H), 7.00–7.40 (m, 8H)

Z-isomer, ^{1}H NMR ($CDCl_3$ + MeOH-d4): 2.75 (t, 2H), 3.56 (t, 2H), 3.95 (t, 2H), 4.09 (t, 2H), 6.79 (d, 2H), 6.91 (d, 2H), 7.01 (d, 2H), 7.05 (d, 2H), 7.16 (d, 2H), 7.19 (d, 2H),

3,4-Bis(4-Chlorophenyl)-4-[4-(2-dimethylaminoethoxy)phenyl]but-3-en-1-ol

E-isomer, ^{1}H NMR ($CDCl_3$): 2.29 (s, 6H), 2.66 (t, 2H), 2.72 (t, 2H), 3.57 (t, 2H), 3.94 (t, 2H), 6.60 (d, 2H), 6.73 (d, 2H), 7.06 (d, 2H), 7.15 (d, 2H), 7.23 (d, 2H), 7.32 (d, 2H)

Z-isomer, HCl-salt, ^{1}H NMR (MeOH-d4):), 2.77 (t, 2H), 3.03 (s, 6H), 3.53 (t, 2H), 3.65 (t, 2H), 4.42 (t, 2H), 6.89 (d, 2H), 7.08 (d, 2H), 7.10 (d, 2H), 7.16 (d, 2H), 7.23 (d, 2H), 7.31 (d, 2H)

4,4-Bis(4-hydroxyphenyl)-3-phenylbut-3-en-1-ol

The protecting tetrahydropyranyl (THP) groups are removed in the dehydration reaction.

^{1}H NMR ($CDCl_3$): 2.76 (t, 2H), 3.54 (m, 2H), 6.46 (d, 2H), 6.70 (d, 2H), 6.80 (d, 2H), 7.0–7.2 (m, 7H)

4-(4-Chlorophenyl)-4-(4-hydroxyphenyl)-3-phenylbut-3-en-1-ol

The protecting THP-group is removed in the dehydration reaction.

E-isomer ^{1}H NMR ($CDCl_3$): 2.65 (t, 2H), 3.45 (t, 2H), 6.29 (d, 2H), 6.49 (d, 2H), 7.00–7.15 (m, 5H), 7.24 (d, 2H), 7.33 (d, 2H)

Z-isomer ^{1}H NMR ($CDCl_3$): 2.79 (t, 2H), 3.58 (t, 2H), 6.80 (d, 2H), 6.81 (d, 2H), 6.97 (d, 2H), 7.1–7.2 (m, 7H)

4-(4-Chlorophenyl)-4-[4-(2,3-dihydroxypropyloxy)phenyl]-3-phenylbut-3-en-1-ol

The 2,2-dimethyl-[1,3]dioxolan ring is cleaved in the reaction.

E-isomer ^{1}H NMR ($CDCl_3$): 2.73 (t, 2H), 3.55 (t, 2H), 3.60–3.77 (m, 2H), 3.87–4.05 (m, 3H), 6.56 (d, 2H), 6.76 (d, 2H), 7.1–7.35 (m, 9H)

3-(4-Hydroxy-1,2-diphenylbut-1-enyl)phenol

The protecting THP-group is removed in the dehydration reaction.

Z-isomer ^{1}H NMR ($CDCl_3$): 2.73 (t, 2H), 3.55 (t, 2H), 6.4–7.4 (m, 12H)

d) Conversion of the hydroxy group of 3,3,4-triarylbut-3-en-1-ols to chlorine

By thionyl chloride

(E)-(2-{4-[4-Chloro-1-(4-fluorophenyl)-2-phenylbut-1-enyl]phenoxy}ethyl-dimethylamine (No.1)

(E)-4-[4-(2-Dimethylaminoethoxy)phenyl]-4-(4-fluorophenyl)-3-phenylbut-3-en-1-ol (0.8 g, 2 mmol) is dissolved in toluene (30 ml) and thionyl chloride (0.7 g, 6 mmol) is added. The mixture is refluxed for an hour.

Toluene is partly evaporated. The crystallized hydrochloride salt of the product is filtered off and the precipitate is washed with toluene. The yield is 0.79 g, 86 %.

^{1}H NMR (HCl salt, MeOH-d4): 2.90 (t, 2H), 2.92 (s, 6H), 3.40 (t, 2H), 3.49 (dist.t, 2H), 4.21 (dist.t, 2H), 6.70 (d, 2H), 6.85 (d, 2H), 7.11 (t, 2H), 7.12–7.22 (m, 5H), 7.32 (dd, 2H)

Using the same method the following compounds are prepared:

(Z)-(2-{4-[4-Chloro-1-(4-fluorophenyl)-2-phenylbut-1-enyl]phenoxy}ethyl-dimethylamine (No. 2)

^{1}H NMR (HCl salt, MeOH-d4): 2.93 (t, 2H), 2.99 (s, 6H), 3.42 (t, 2H), 3.61 (dist.t, 2H), 4.39 (dist.t, 2H), 6.73 (t, 2H), 6.88 (dd, 2H), 7.07 (d, 2H), 7.12–7.22 (m, 5H), 7.29 (d, 2H)

(E)-(2-{4-[4-Chloro-1-(4-chlorophenyl)-2-phenylbut-1-enyl]phenoxy}-ethyl)dimethylamine (No. 3)

^{1}H NMR ($CDCl_3$): 2.30 (s, 6H), 2.66 (t, 2H), 2.91 (t, 2H), 3.40 (t, 2H), 3.94 (t, 2H), 6.57 (d, 2H), 6.75 (d, 2H), 7.1–7.4 (m, 9H)

(2-{4-[4-Chloro-1,2-bis(4-chlorophenyl)but-1-enyl]phenoxy}ethyl)dimethylamine (No. 4 and 5)

E-isomer (No. 4), HCl-salt, ^{1}H NMR ($CDCl_3$): 2.90 (s, 6H), 2.94 (t, 2H), 3.40 (t, 4H), 4.38 (t, 2H), 6.59 (d, 2H), 6.78 (d, 2H), 7.06 (d, 2H), 7.19 (d, 2H), 7.23 (d, 2H), 7.35 (d, 2H)

Z-isomer (No. 5), HCl-salt, ^{1}H NMR (MeOH-d4):), 2.95 (t, 2H), 3.41 (s, 6H), 3.41 (t, 2H), 3.48-3.58 (m, 2H) 4.56-4.65 (m, 2H), 6.79 (d, 2H), 6.92 (d, 2H), 7.02 (d, 2H), 7.05 (d, 2H), 7.19 (d, 2H), 7.22 (d, 2H)

(E)-1-[4-(2-Benzyloxyethoxy)phenyl]-4-chloro-1-(4-fluorophenyl)-2-phenyl-but-1-ene

^{1}H NMR ($CDCl_3$): 2.92 (t, 2H), 3.41 (t, 2H), 3.74 (dist.t, 2H), 4.01 (dist.t, 2H), 4.59 (s, 2H), 6.58 (d, 2H), 6.76 (d, 2H), 7.06 (t, 2H), 7.10–7.40 (m, 12H)

(E)-1-[4-(2-Benzyloxyethoxy)phenyl]-4-chloro-1,2-bis(4-chlorophenyl)-but-1-ene

^{1}H NMR ($CDCl_3$): 2.90 (t, 2H), 3.39 (t, 2H), 3.76 (dist.t, 2H), 4.04 (dist.t, 2H), 4.60 (s, 2H), 6.60 (d, 2H), 6.74 (d, 2H), 7.06 (d, 2H), 7.17 (d, 2H), 7.23 (d, 2H) 7.25–7.4 (m, 7H)

4-Chloro-1-[4-(2-chloroethoxy)phenyl]-1,2-bis(4-chlorophenyl)-but-1-ene (No. 6 and 7)

is prepared from 3,4-bis(4-chlorophenyl)-4-[4-(2-hydroxyethoxy)phenyl]but-3-en-1-ol.

E-isomer (No.6), ^{1}H NMR ($CDCl_3$): 2.90 (t, 2H), 3.39 (m, 2H), 3.73 (t, 2H), 4.10 (t, 2H), 6.59 (d, 2H), 6.76 (d, 2H), 7.10 (d, 2H), 7.17 (d, 2H), 7.23 (d, 2H), 7.33 (d, 2H)

Z-isomer (No. 7), ^{1}H NMR ($CDCl_3$): 2.94 (t, 2H), 3.40 (t, 2H), 3.83 (t, 2H), 4.25 (t, 2H), 6.79 (d, 2H), 6.92 (d, 2H), 7.02 (d, 2H), 7.05 (d, 2H), 7.18 (d, 2H), 7.20 (d, 2H)

By triphenylphosphine-carbon tetrachloride

1-(2,2-Dimethyl-[1,3]dioxolan-4-ylmethoxy)phenyl-4-chloro-1-(4-chloro-phenyl)-2-phenyl-but-1-ene

Triphenyl phosphine (0.19 g, 0.73 mmol) is dissolved in acetonitrile (4 ml). Carbon tetrachloride (0.237 g, 1.3 mmol) and triethylamine (0.043 g, 0.43 mmol) is added to the solution and the mixture is stirred for half an hour at ambient temperature. 4-(2,2-Dimethyl-[1,3]dioxolan-4-ylmethoxy)phenyl-4-(4-chlorophenyl)-3-phenyl-but-3-en-1-ol (0.2 g, 0.43 mmol, prepared from 4-(4-chlorophenyl)-4-[4-(2,3-dihydroxypropyloxy)phenyl]-3-phenylbut-3-n-1-ol by protecting the diol group as acetonide) is dissolved in acetonitrile, added to the reaction mixture and stirring is continued for additional 2 hours. Then the solvent is evaporated and the residue is dissolved in 20 ml of methanol-water-solution (8:2). Solution is extracted twice with petroleum ether (20 ml) at boiling point. Petroleum ether phases are combined and washed once again with hot methanol-water solution. Yield 0.07 g.

E-isomer ^{1}H NMR ($CDCl_3$): 1.37 and 1.41 (2s, together 6H), 2.91 (t, 2H), 3.40 (t, 2H), 3.70–4.14 (m, 4H), 4.39 (quintet, 1H), 6.56 (d, 2H), 6.76 (d, 2H), 7.05–7.4 (m, 9H)

e) Removal of the protecting groups

(E)-2-{4-[4-Chloro-2-phenyl-1-(4-fluorophenyl)but-1-enyl]phenoxy}ethanol (No. 8)

(E)-1-[4-(2-Benzyloxyethoxy)phenyl]-4-chloro-1-(4-fluorophenyl)-2-phenylbut-1-ene (400 mg, 0.8 mmol) is dissolved in toluene. Zn (106 mg, 1.6 mmol) and acetyl chloride (126 mg, 1.6 mmol) are added under nitrogen atmosphere. The mixture is stirred at room temperature for 6 h. The mixture is filtered and the solvent evaporated. The residue is dissolved in 80 % aqueous

methanol containing 5 % of sodium hydroxide. The mixture is stirred at room temperature for 2 h and methanol is evaporated. Some water is added and the product is extracted into ethyl acetate. The mixture is dried and the solvent is evaporated. The product is purified by flash chromatography (eluent toluene:methanol 9:1).

^{1}H NMR ($CDCl_3$): 2.92 (t, 2H,), 3.41 (t, 2H), 3.87-3.95 (m, 4H), 6.57 (d, 2H), 6.78 (d, 2H), 7.06 (t, 2H), 7.10–7.31 (m, 7H)

Using the same method the following compound included in the invention is prepared:

(E)-2-{4-[(Z)-4-Chloro-1,2-bis(4-chlorophenyl)but-1-enyl]phenoxy}ethanol (No. 9)

^{1}H NMR ($CDCl_3$): 2.90 (t, 2H), 3.39 (t, 2H), 3.85–4.05 (m, 4H), 6.61 (d, 2H), 6.77 (d, 2H), 7.07 (d, 2H), 7.1–7.26 (m, 4H), 7.35 (d, 2H)

(E)-3-{4-[(Z)-4-Chloro-1-(4-chlorophenyl)-2-phenyl-but-1-enyl]phenoxy}-propane-1,2-diol (No. 10)

1-(2,2-Dimethyl-[1,3]dioxolan-4-ylmethoxy)phenyl-4-chloro-1-(4-chlorophenyl)-2-phenyl-but-1-ene (0.5 g, 1.0 mmol) is dissolved in ethanol and 2 N aqueous hydrogen chloride (5 ml) is added to the solution. The mixture is heated to 40 °C and stirring is continued for an hour. Then ethanol is evaporated and the product is extracted in toluene, which is washed with water, dried and evaporated to dryness. Yield 0.45 g.

^{1}H NMR ($CDCl_3$): 2.91 (t, 2H), 3.41 (t, 2H), 3.60-4.15 (m, 5H), 6.56 (d, 2H), 6.77 (d, 2H), 7.1–7.4 (m, 9H)

Example 2

a) O-alkylation of 4-(1,2-diaryl-4-hydroxybut-1-enyl)phenol derivatives

4,4-Bis[4-(2-benzyloxyethoxy)phenyl]-3-phenyl but-3-en-1-ol

is prepared from 4,4-bis(4-hydroxyphenyl)-3-phenylbut-3-en-1-ol (example 1c) and benzyl 2-bromoethyl ether by PTC reaction according to the method described in the example 1a.

^{1}H NMR ($CDCl_3$): 2.78 (t, 2H), 3.59 (q, 2H), 3.74, 3.84, 4.02 and 4.17 (4 dist.t, together 8H), 4.59 (s, 2H), 4.65 (s, 2H), 6.56 (d, 2H), 6.76 (d, 2H), 6.91 (d, 2H), 7.09–7.40 (m, 17H)

Using the same method the following compounds are prepared:

(E)-4-[4-(2-Benzyloxyethoxy)phenyl]-4-(4-chlorophenyl)-3-phenyl-but-3-en-1-ol

^{1}H NMR ($CDCl_3$): 2.74 (t, 2H), 3.56 (t, 2H), 3.71–3.76 (m, 2H), 3.98–4.03 (m, 2H), 4.60 (s, 2H), 6.57 (d, 2H), 6.75 (d, 2H), 7.10–7.40 (m, 14H)

(Z)-4-[3-(2-Benzyloxyethoxy)phenyl]-3,4-diphenyl-but-3-en-1-ol

^{1}H NMR ($CDCl_3$): 2.75 (t, 2H), 3.58 (t, 2H), 3.63–3.66 (m, 2H), 3.81-3.85 (m, 2H), 4.55 (s, 2H), 6.47–7.40 (m, 19H)

(Z)-4-[4-(2-Methylsulfanylethoxy)phenyl]-3,4-diphenyl-but-3-en-1-ol

The compound is prepared by using the method described in the example 1a starting from 4-(4-hydroxyphenyl)-3,4-diphenyl-but-3-en-1-ol (preparation described in US patent no. 4,996,225) and 2-chloroethyl methyl sulfide.

^{1}H NMR ($CDCl_3$): 2.16 (s, 3H), 2.75 (t, 2H), 2.79 (t, 2H), 3.59 (q, 2H), 4.02 (t, 2H), 6.55 (d, 2H), 6.79 (d, 2H), 7.05-7.40 (m, 10H)

(Z)-4-[4-(3-Benzyloxypropoxy)phenyl]-3,4-diphenyl-but-3-en-1-ol

is prepared by the same method using benzyl 3-bromopropyl ether as a reagent.

^{1}H NMR ($CDCl_3$): 2.00 (quint., 2H), 2.75 (t, 2H), 3.59 (2x t, 4H), 3.95 (t, 2H), 4.48 (s, 2H), 6.54 (d, 2H), 6.78 (d, 2H), 7.11–7.40 (m, 15H)

(E)-4-(4-Chlorophenyl)-3-phenyl-4-(4-{2-[2-(tetrahydropyranyloxy)ethoxy]-ethoxy}phenyl)but-3-en-1-ol

NaH (0.09 g, 2.69 mmol) is mixed with dimethylformamide (DMF) (30 ml). (E)-4-(4-Chlorophenyl)-4-(4-hydroxyphenyl)-3-phenylbut-3-en-1-ol is dissolved in the solution and the mixture is heated to 60 °C and stirred for half an hour. 2-[(2-(Tetrahydropyranyloxy)ethoxy]ethyl chloride (0.83 g, 4.03 mmol) dissolved in DMF (5 ml) is added to the solution and heating is continued for 3 hours. Saturated aqueous ammonium chloride solution (30 ml) and toluene (30 ml) is added to the cooled reaction mixture and stirring is continued for 10 minutes. Layers are separated and aqueous layer is extracted with toluene (30 ml). Toluene phases are combined and washed with 2 N aqueous sodium hydroxide and three times with water. Organic phase is dried and evaporated to dryness. Yield 1.4 g, 99 %.

^{1}H NMR ($CDCl_3$): 1.40–1.90 (m, 6H), 2.70 (t, 2H), 3.4-3.94 (m, 10H), 3.95–4.05 (m, 2H), 4.55 (m, 1H), 6.56 (d, 2H), 6.74 (d, 2H), 7.05–7.35 (m, 9H)

Using the same method the following compounds are prepared:

(Z)-3,4-Diphenyl-4-(4-{2-[(2-(tetrahydropyranyloxy)ethoxy]-ethoxy}phenyl)but-3-en-1-ol

is prepared by the same method as previous compound starting from 4-(4-hydroxyphenyl)-3,4-diphenyl-but-3-en-1-ol (preparation described in US patent no. 4,996,225) and 2-[2-(tetrahydropyranyloxy)ethoxy]ethyl chloride

^{1}H NMR ($CDCl_3$): 1.40-1.91 (m, 6H), 2.74 (t, 2H), 3.4–4.0 (m, 12H), 4.61 (m, 1H), 6.55 (d, 2H), 6.77 (d, 2H), 7.05–7.35 (m, 10H)

4-(4-Fluorophenyl)-3-phenyl-4-(4-{2-[2-(tetrahydropyranyloxy)ethoxy]-ethoxy}phenyl)but-3-en-1-ol

E-isomer ^{1}H NMR ($CDCl_3$): 1.38–1.90 (m, 6H), 2.75 (t, 2H), 3.32–4.03 (m, 10H), 4.00 (m, 2H), 4.62 (m, 1H), 6.56 (d, 2H), 6.75 (d, 2H), 7.04 (t, 2H), 7.00–7.20 (m, 5H), 7.27 (dd, 2H)

Z-isomer ^{1}H NMR ($CDCl_3$): 1.40–1.90 (m, 6H), 2.79 (t, 2H), 3.43-4.03 (m, 10H), 4.15 (m, 2H), 4.65 (m, 1H), 6.69 (t, 2H), 6.83 (dd, 2H), 6.90 (d, 2H), 7.05–7.20 (m, 5H), 7.19 (d, 2H)

(Z)-4-[4-(2,2-Dimethyl-[1,3]-dioxolan-4-ylmethoxy)phenyl]-3,4-diphenylbut-3-en-1-ol

^{1}H NMR ($CDCl_3$): 1.37 and 1.41 (2s, together 6H), 2.75 (t, 2H), 3.58 (t, 2H), 3.70–4.10 (m, 4H), 4.39 (quintet, 1H), 6.56 (d, 2H), 6.78 (d, 2H), 7.10–7.40 (m, 10H)

{4-[1-(4-Chlorophenyl)-4-hydroxy-2-phenylbut-1-enyl]phenoxy}acetic acid ethyl ester

is prepared from 4-(4-chlorophenyl)-4-(4-hydroxyphenyl)-3-phenylbut-3-en-1-ol (example 1c.) and ethyl bromoacetate according to the procedure described in the example 1a using NaH as a base.

E-isomer ^{1}H NMR ($CDCl_3$): 1.25 (t, 3H), 2.74 (t, 2H), 3.57 (t, 2H), 4.22 (q, 2H), 4.48 (s, 2H), 6.56 (d, 2H), 6.77 (d, 2H), 7.0–7.4 (m, 9H)

Z-isomer ^{1}H NMR ($CDCl_3$): 1.31 (t, 3H), 2.78 (t, 2H), 3.58 (t, 2H), 4.29 (q, 2H), 4.63 (s, 2H), 6.79 (d, 2H), 6.89 (d, 2H), 6.98 (d, 2H), 7.15–7.30 (m, 7H)

b) Conversion of the hydroxyl group to chlorine

1,1-Bis[4-(2-benzyloxyethoxy)phenyl]-4-chloro-2-phenyl-but-1-ene

Conversion of the hydroxy group to chlorine is carried out using thionyl chloride as a reagent according to the procedure described in the example 1d.

^{1}H NMR ($CDCl_3$): 2.94 (t, 2H), 3.42 (t, 2H), 3.73 and 3.83 (2 dist.t., together 4H), 4.00 and 4.16 (2 dist.t., together 4H), 4.58 (s, 2H), 4.65 (s, 2H), 6.56 (d, 2H), 6.76 (d, 2H), 6.92 (d, 2H), 7.10–7.40 (m, 17H)

Using the same method the following compounds are prepared:

(E)-1-[4-(2-Benzyloxyethoxy)phenyl]-4-chloro-1-(4-chlorophenyl)-2-phenyl-but-1-ene

^{1}H NMR ($CDCl_3$): 2.91 (t, 2H), 3.40 (t, 2H), 3.71–3.76 (m, 2H), 3.98–4.03 (m, 2H), 4.60 (s, 2H), 6.57 (d, 2H), 6.75 (d, 2H), 7.10–7.40 (m, 14H)

(Z)-4-Chloro-1-[4-(2-methylsulfanylethoxy)phenyl]-1,2-diphenyl-but-1-ene (No. 11)

^{1}H NMR ($CDCl_3$): 2.16 (s, 3H), 2.79 (t, 2H), 2.92 (t, 2H), 3.42 (t, 2H), 4.01 (t, 2H), 6.55 (d, 2H), 6.78 (d, 2H), 7.05–7.45 (m, 10H)

(Z)-1-[3-(2-Benzyloxyethoxy)phenyl]-4-chloro-1,2-diphenyl-but-1-ene

^{1}H NMR ($CDCl_3$): 2.92 (t, 2H), 3.41 (t, 2H), 3.63–3.67 (m, 2H), 3.81–3.85 (m, 2H), 4.55 (s, 2H), 6.47-7.40 (m, 19H)

(Z)-1-[4-(3-Benzyloxypropoxy)phenyl]- 4-chloro-1,2-diphenyl-but-1-ene

^{1}H NMR ($CDCl_3$): 2.0 (quintet, 2H), 2.92 (t, 2H), 3.42 (t, 2H), 3.59 (t, 2H), 3.94 (t, 2H), 4.48 (s, 2H), 6.54 (d, 2H), 6.78 (d, 2H), 7.11–7.40 (m, 15H)

{4-[4-Chloro-1-(4-chlorophenyl)-2-phenylbut-1-enyl]phenoxy}acetic acid ethyl ester and the corresponding acid (No. 12 and 13)

E-isomer, ethyl ester ^{1}H NMR ($CDCl_3$): 1.25 (t, 3H), 2.91 (t, 2H), 3.41 (t, 2H), 4.21 (q, 2H), 4.49 (s, 2H), 6.57 (d, 2H), 6.77 (d, 2H), 7.0–7.4 (m, 9H)

The ester is hydrolyzed to the corresponding acid in 80 % aqueous methanol containing 5 % of sodium hydroxide.

E-isomer, acid (No. 12) ^{1}H NMR ($CDCl_3$): 2.91 (t, 2H), 3.41 (t, 2H), 4.47 (s, 2H), 6.58 (d, 2H), 6.78 (d, 2H), 7.0–7.4 (m, 9H)

Z-isomer, ethyl ester ^{1}H NMR ($CDCl_3$): 1.31 (t, 3H), 2.95 (t, 2H), 3.42 (t, 2H), 4.30 (q, 2H), 4.65 (s, 2H), 6.79 (d, 2H), 6.91 (d, 2H), 6.98 (d, 2H), 7.15–7.30 (m, 7H)

Z-isomer, acid (No. 13) ^{1}H NMR ($CDCl_3$): 2.95 (t, 2H), 3.41 (t, 2H), 4.65 (s, 2H), 6.79 (d, 2H), 6.94 (d, 2H), 6.98 (d, 2H), 7.10–7.30 (m, 7H)

(Z)-1,2-Diphenyl-4-chloro-4-(4-{2-[2-(tetrahydropyranyloxy)ethoxy]-ethoxy}phenyl)-but-1-ene

Conversion of hydroxy group to chlorine is carried out using Ph_3P and CCl_4 as reagents according to the procedure described in the example 1d.

^{1}H NMR ($CDCl_3$): 1.30–1.90 (m, 6H), 2.92 (t, 2H), 3.42 (t, 2H), 3.4–4.0 (m, 10H), 4.62–4.65 (m, 1H), 6.55 (d, 2H), 6.77 (d, 2H), 7.05–7.35 (m, 10H)

Using the same method the following compounds are prepared:

(Z)-4-[4-(4-Chloro-1,2-diphenyl-but-1-enyl)phenoxymethyl]-2,2-dimethyl-[1,3]dioxolane

^{1}H NMR ($CDCl_3$): 1.37 and 1.41 (2s, together 6H), 2.91 (t, 2H), 3.41 (t, 2H), 3.7–4.1 (m, 4H), 4.39 (quintet, 1H), 6.55 (d, 2H), 6.77 (d, 2H), 7.10–7.41 (m, 10H)

(E)-1-(4-{2-[(2-Chloroethoxy]ethoxy}phenyl)-4-chloro-1-(4-chloro-phenyl)-2-phenyl-but-1-ene (No. 14)

The tetrahydropyranyloxy group is also converted to chlorine in the reaction.

^{1}H NMR ($CDCl_3$): 2.94 (t, 2H), 3.43 (t, 2H), 3.65 (dist. t, 2H), 3.8-3.85 (m, 4H), 4.0–4.06 (m, 2H), 6.60 (d, 2H), 6.78 (d, 2H), 7.10–7.40 (m, 9H)

(E)-1-(4-{2-[(2-Chloroethoxy]ethoxy}phenyl)-4-chloro-1-(4-fluoro-phenyl)-2-phenyl-but-1-ene (No. 15)

The tetrahydropyranyloxy group is also converted to chlorine in the reaction.

^{1}H NMR ($CDCl_3$): 2.91 (t, 2H), 3.41 (t, 2H), 3.62 (dist. t, 2H), 3.74–3.85 (m, 4H), 4.01 (dist.t, 2H), 6.57 (d, 2H), 6.76 (d, 2H), 7.06 (t, 2H), 7.09–7.22 (m, 5H), 7.27 (dd, 2H)

c) Removal of the protecting groups

2-(4-{4-Chloro-1-[4-(2-hydroxyethoxy)phenyl]-2-phenyl-but-1-enyl}-phenoxy)-1-ethanol (No. 16)

The benzyl groups are removed using Zn and AcCl as reagents according to the method described in the example 1e.

^{1}H NMR ($CDCl_3$): 2.95 (t, 2H), 3.42 (t, 2H), 3.80–4.20 (m, 8H), 6.56 (d, 2H), 6.78 (d, 2H), 6.92 (d, 2H), 7.10–7.26 (m, 7H)

Using the same method the following compounds included in the invention are prepared:

(E)-2-{4-[4-Chloro-2-phenyl-1-(4-chlorophenyl)but-1-enyl]phenoxy}ethanol (No. 17)

^{1}H NMR ($CDCl_3$): 2.92 (t, 2H), 3.41 (t, 2H), 3.80–4.00 (m, 4H), 6.57 (d, 2H), 6.77 (d, 2H), 7.10–7.40 (m, 9H)

(Z)-2-[3-(4-Chloro-1,2-diphenyl-but-1-enyl)phenoxy]ethanol (No. 18)

^{1}H NMR ($CDCl_3$): 2.93 (t, 2H), 3.41 (t, 2H), 3.70–3.80 (m, 4H), 6.40–7.40 (m, 14 H)

(Z)-2-{2-[4-(4-Chloro-1,2-diphenylbut-1-enyl)phenoxy]ethoxy}ethanol (No. 19)

The tetrahydropyranyl ether is cleaved with H^+/EtOH using the method described in the example 1e.

^{1}H NMR ($CDCl_3$): 2.92 (t, 2H), 3.41 (t, 2H), 3.61, 3.68, 3.77 (3 dist.t, 6H), 4.00 (dist.t, 2H), 6.56 (d, 2H), 6.78 (d, 2H), 7.1–7.4 (m, 10H)

Using the same method the following compound included in the invention is prepared:

(Z)-3-[4-(4-Chloro-1,2-diphenyl-but-1-enyl)phenoxy]propane-1,2-diol (No. 20)

^{1}H NMR ($CDCl_3$): 2.92 (t, 2H), 3.41 (t, 2H), 3.58–4.10 (m, 5H), 6.53 (d, 2H), 6.78 (d, 2H), 7.10–7.41 (m, 10H)

Example 3

a) (Z)-4-[4-(2-Imidazol-1-yl-ethoxy)phenyl]-3,4-diphenyl-but-3-en-1-ol

(Z)-4-[4-(2-Bromoethoxy)phenyl]-3,4-diphenylbut-3-en-1-ol (preparation described in US patent no. 4,996,225) (4.97 g, 0.0117 mol) is dissolved in methyl ethyl ketone (50 ml) and potassium carbonate (4.8 g, 0.035 mol) and imidazole sodium salt (2.11 g, 0.0234 mol) is added to the solution. Mixture is stirred and refluxed for five hours. Then the solution is filtered and the filtrate is evaporated to dryness. The residue is dissolved in ethyl acetate,

washed with 2 N aqueous sodium hydroxide solution and with water, dried and evaporated to dryness. The residue is recrystallized from the mixture of toluene and acetonitrile.

^{1}H NMR ($CDCl_3$): 2.75 (t, 2H), 3.59 (dist. t, 2H), 4.07 (dist. t, 2H), 4.23 (dist. t, 2H), 6.51 (d, 2H), 6.79 (d, 2H), 6.97 (s, 1H), 7.03 (s, 1H), 7.05-7.40 (m, 10H), 7.51 (s, 1H)

(Z)-4-[4-(2-Methylaminoethoxy)phenyl]-3,4-diphenylbut-3-en-1-ol

(Z)-4-[4-(2-Chloroethoxy)phenyl]-3,4-diphenylbut-3-en-1-ol (prepared as preparation of (Z)-4-[4-(2-bromoethoxy)phenyl]-3,4-diphenylbut-3-en-1-ol which is described in US patent no. 4,996,225)(2.0 g, 0.0052 mol) and methyl amine in 40 % aqueous solution (5 ml, 0.065 mol) is mixed with dimethylformamide (8 ml). Mixture is heated in a sealed tube at 60 °C for 8 hours. To the mixture is added 60 ml of water and extracted with ethyl acetate. Ethyl acetate phase is washed with aqueous 2 N hydrogen chloride solution. Water phase is made alkaline with 2 N sodium hydroxide solution and extracted with ethyl acetate. Ethyl acetate phase is washed with water, dried with magnesium sulfate and evaporated to dryness. Yield 1.5 g.

^{1}H NMR ($CDCl_3$): 2.39 (s, 3H), 2.70 (t, 2H), 2.84 (t, 2H), 3.48 (t, 2H), 3.93 (t, 2H), 6.59 (d, 2H), 6.77 (d, 2H), 7.10–7.40 (m, 10H)

b) (Z)-4-(4-{2-[(2-Benzyloxyethyl)methylamino]ethoxy}phenyl)-3,4-diphenyl-but-3-en-1-ol

Prepared by using the same PTC method as in the example 1a using benzyl 2-bromoethyl ether as a reagent.

^{1}H NMR ($CDCl_3$): 2.35 (s, 3H), 2.70, 2.75, 2,79 (3 t, 6H), 3.56 (t, 2H), 3.60 (t, 2H), 3.94 (t, 2H), 4.50 (s, 2H), 6.54 (d, 2H), 6.77 (d, 2H), 7.10–7.20 (m, 5H), 7.25–7.35 (m, 10H)

c) (Z)-1-{2-[4-(4-Chloro-1,2-diphenylbut-1-enyl)phenoxy]ethyl}-1H-imidazole (No. 21)

is prepared according to the example 1d using triphenylphosphine and carbon tetrachloride as reagents. Purification of product is made by evaporating acetonitrile and dissolving the residue to acidic methanol-water (8:2) solution and extracting triphenylphosphine with toluene (three times, at room temperature). Methanol-water-solution was made alkaline and the product was extracted with toluene. Toluene phase was washed twice with water and evaporated to dryness. The product was crystallized from ethyl acetate as HCl-salt. Yield 46 %.

^{1}H NMR (HCl-salt, MeOH-d4): 2.89 (t, 2H), 3.39 (t, 2H), 4.23 (t, 2H), 4.60 (t, 2H), 6.60 (d, 2H), 6.80 (d, 2H), 7.10–7.40 (m, 10H), 7.54 (s, 1H), 7.67 (s, 1H), 8.98 (s, 1H)

(Z)-(2-Benzyloxyethyl)-{2-[4-(4-chloro-1,2-diphenyl-but-1-enyl)phenoxy-ethyl}methylamine

is prepared according to example 1d using thionyl chloride as a reagent.

^{1}H NMR ($CDCl_3$): 2.35 (s, 3H), 2.70, 2.79 (2 t, 4H), 2.92 (t, 2H), 3.42 (t, 2H), 3.56 (t, 2H), 3.93 (t, 2H), 4.51 (s, 2H), 6.54 (d, 2H), 6.77 (d, 2H), 7.10–7.40 (m, 15H)

d) (Z)-2-({2-[-4-(4-Chloro-1,2-diphenyl-but-1-enyl)phenoxy]ethyl}-methylamino)ethanol (No. 22)

is prepared by the same method as 1e using Zn and acetyl chloride as reagents.

^{1}H NMR ($CDCl_3$): 2.32 (s, 3H), 2.60 (t, 2H), 2.78 (t, 2H), 2.92 (t, 2H), 3.42 (t, 2H), 3.57 (t, 2H), 3.91 (t, 2H), 6.54 (d, 2H), 6.78 (d, 2H), 7.05–7.40 (m, 10H)

Example 4

a) 2-(4-Chlorophenyl)-1-(4-methoxyphenyl)ethanone

Anisole (13.9 g, 0.13 mol) is added to a stirred solution of 4-chlorophenylacetic acid (20.0 g, 0.12 mol) in trifluoroacetic anhydride (16.5 ml, 0.12 mol). The mixture is stirred in room temperature for 24 h. Ice water is added and the crystallized product is collected on a sinter and washed with water. The product is recrystallized from ethanol. The yield is 20.4 g, 67 %.

^{1}H NMR ($CDCl_3$): 3.86 (s, 3H), 4.20 (s, 2H), 6.93 (d, 2H), 7.20 (d, 2H), 7.28 (d, 2H), 7.98 (d, 2H)

Using the same method the following compounds are prepared:

2-(4-Fluorophenyl)-1-(4-methoxyphenyl)ethanone

^{1}H NMR ($CDCl_3$): 3.87 (s, 3H), 4.21 (s, 2H), 6.94 (d, 2H), 7.01 (t, 2H), 7.22 (dd, 2H), 7.99 (d, 2H)

1-(4-Methoxyphenyl)-2-phenyl-ethanone

^{1}H NMR ($CDCl_3$): 3.84 (s, 3H), 4.23 (s, 2H), 6.92 (d, 2H), 7.20–7.40 (m, 5H), 7.99 (d, 2H)

b) 2-(4-Chlorophenyl)-1-(4-hydroxyphenyl)ethanone

Aluminum chloride (29.8 g, 0.223 mol) is added in small portions to a stirred solution of 2-(4-chlorophenyl)-1-(4-methoxyphenyl)ethanone (19.4 g, 0.074 mol) in toluene (300 ml). The mixture is heated to 60 °C and stirring is continued for 2 h. Dilute hydrochloric acid is added to the cooled mixture. Ethyl acetate is added to dissolve the product. The layers are separated and the aqueous phase is extracted with ethyl acetate. The combined organic phases are dried and the solvents are evaporated. The product is recrystallized from toluene. The yield is 17 g, 93 %.

^{1}H NMR ($CDCl_3$ + MeOH-d4): 4.19 (s, 2H), 6.85 (d, 2H), 7.19 (d, 2H), 7.28 (d, 2H), 7.90 (d, 2H)

Using the same method the following compounds are prepared:

2-(4-Fluorophenyl)-1-(4-hydroxyphenyl)ethanone

^{1}H NMR ($CDCl_3$ + MeOH-d4): 4.20 (s, 2H), 6.86 (d, 2H), 7.00 (t, 2H), 7.22 (dd, 2H), 7.91 (d, 2H)

1-(4-Hydroxyphenyl)-2-phenyl ethanone

^{1}H NMR ($CDCl_3$ + MeOH-d4): 4.20 (s, 2H), 6.84 (d, 2H), 7.2–7.4 (m, 5H) 7.90 (d, 2H)

c) O-Alkylation of 4-hydroxydesoxybenzoin derivatives

In PTC-conditions

2-(4-Chlorophenyl)-1-[4-(2-dimethylaminoethoxy)phenyl]ethanone

10 % Aqueous sodium hydroxide is added to the mixture containing 2-(4-chlorophenyl)-1-(4-hydroxyphenyl)ethanone (6.0 g, 0.024 mol), TBABr (0.9 g) in toluene (60 ml) at 60 °C. The mixture is stirred for 30 min. N,N-Dimethylaminoethyl chloride hydrochloride (3.6 g, 0.025 mol) is added and stirring is continued at 70–75 °C for 3 h. The layers are separated and the aqueous phase is extracted with toluene. The combined toluene phases are evaporated to give the product (1.85 g, 24 %).

^{1}H NMR ($CDCl_3$): 2.34 (s, 6H), 2.75 (t, 2H), 4.12 (t, 2H), 4.20 (s, 2H), 6.95 (d, 2H), 7.19 (d, 2H), 7.29 (d, 2H), 7.97 (d, 2H)

Using the same method the following compound is prepared:

1-[4-(2-Dimethylaminoethoxy)phenyl]-2-(4-fluorophenyl)ethanone

^{1}H NMR ($CDCl_3$): 2.34 (s, 6H), 2.75 (t, 2H), 4.12 (t, 2H), 4.21 (s, 2H), 6.96 (d, 2H), 7.01 (t, 2H), 7.22 (dd, 2H), 7.98 (d, 2H)

With K_2CO_3 in 2-butanone

1-[4-(2-Benzyloxyethoxy)phenyl]-2-phenyl ethanone

1-(4-Hydroxyphenyl)-2-phenyl ethanone (17 g, 0.08 mol) is dissolved in 2-butanone (200 ml) and potassium carbonate (33.1 g, 0.24 mol) and 2-benzyloxyethyl bromide (25.8 g, 0.12 mol) is added to the solution. Mixture is stirred and refluxed for three hours. Then the solution is filtered and the

filtrate is evaporated to dryness. The residue is dissolved in toluene, washed with 2 N aqueous sodium hydroxide solution and with water, dried and evaporated to dryness. The product is crystallized from ethanol. Yield 23.2 g, 84 %.

^{1}H NMR ($CDCl_3$): 3.80-3.86 (m, 2H), 4.20–4.22 (m, 2H), 4.23 (s, 2H), 4.63 (s, 2H), 6.90 (d, 2H), 7.20–7.40 (m, 10H), 7.90 (d, 2H)

Using the same method the following compounds are prepared:

1-[4-(2-Benzyloxyethoxy)phenyl]-2-(4-chlorophenyl)ethanone

^{1}H NMR ($CDCl_3$): 3.84 (dist.t., 2H), 4.20 (dist.t., 2H), 4.20 (s, 2H), 4.63 (s, 2H), 6.95 (d, 2H), 7.19 (d, 2H), 7.29 (d, 2H), 7.30–7.45 (m, 5H), 7.96 (d, 2H)

2-(3-Methoxyphenyl)-1-[4-(2-piperidin-1-ylethoxy)phenyl]ethanone

1-(4-hydroxyphenyl)-2-(3-methoxyphenyl)ethanone and 1-(2-chloroethyl)piperidine hydrochloride are used as starting materials.

^{1}H NMR ($CDCl_3$): 1.37-1.52 (m, 2H), 1.52–1.68 (m, 4H), 2.50 (br.t, 4H), 2.78 (t, 2H), 3.77 (s, 3H), 4.14 (t, 2H), 4.19 (s, 2H), 6.73-6.90 (m, 3H), 6.90 (d, 2H), 7.22 (t, 1H), 7.96 (d, 2H)

2-(2-Methoxyphenyl)-1-[4-(2-piperidin-1-ylethoxy)phenyl]ethanone

1-(4-hydroxyphenyl)-2-(2-methoxyphenyl)ethanone and 1-(2-chloroethyl)piperidine hydrochloride are used as starting materials.

^{1}H NMR ($CDCl_3$): 1.40-1.53 (m, 2H), 1.53–1.70 (m, 4H), 2.51 (br.t, 4H), 2.79 (t, 2H), 3.79 (s, 3H), 4.16 (t, 2H), 4.22 (s, 2H), 6.84–7.00 (m, together 4H) under which 6.92 (d, 2H), 7.14-7.30 (m, 2H), 8.00 (d, 2H)

d) C-Alkylation of desoxybenzoin derivatives

4-Benzyloxy-2-(4-chlorophenyl)-1-[4-(2-dimethylaminoethoxy)phenyl]butan-1-one

The mixture containing 2-(4-chlorophenyl)-1-[4-(2-dimethylamino-ethoxy)phenyl]ethanone (6.3 g, 0.020 mol) and TBABr (0.5 g) in toluene (70 ml) is heated to 70 °C and 48 % aqueous sodium hydroxide (70 ml) is added. The mixture is stirred for 30 min. and (2-bromoethoxymethyl)benzene (5.5 g, 0.025 mol) is added dropwise at 85–90 °C. The reaction mixture is stirred at 95–100 °C for 3 h. The layers are separated and the aqueous phase is extracted with toluene. The combined organic phases are washed with water and the solvent is evaporated. The residual product (9.0 g) is used in the next reaction step without further purification.

^{1}H NMR ($CDCl_3$): 1.93–2.15 and 2.38–2.58 (2m, together 2H), 2.32 (s, 6H), 2.72 (t, 2H), 3.25–3.55 (m, 2H), 4.08 (t, 2H), 4.42 (s, 2H), 4.82 (t, 1H), 6.88 (d, 2H), 7.15–7.40 (m, 9H), 7.92 (d, 2H)

Using the same method the following compounds are prepared:

4-Benzyloxy-1-[4-(2-dimethylaminoethoxy)phenyl]-2-(4-fluorophenyl)butan-1-one

^{1}H NMR ($CDCl_3$): 1.95–2.15 and 2.40-2.60 (2m, together 2H), 2.31 (s, 6H), 2.71 (t, 2H), 3.25–3.55 (m, 2H), 4.07 (t, 2H), 4.42 (s, 2H), 4.83 (t, 1H), 6.88 (d, 2H), 6.94 (t, 2H), 7.10–7.40 (m, 7H), 7.93 (d, 2H)

4-Benzyloxy-2-(4-chlorophenyl)-1-(4-methoxyphenyl)butan-1-one

^{1}H NMR ($CDCl_3$): 1.95–2.15 and 2.35-2.55 (2m, together 2H), 3.30–3.55 (m, 2H), 3.82 (s, 3H), 4.42 (s, 2H), 4.82 (t, 1H), 6.85 (d, 2H), 7.10–7.40 (m, 9H), 7.93 (d, 2H)

1-[4-(2-Benzyloxyethoxy)phenyl]-2-phenyl-4-(tetrahydropyranyloxy)butan-1-one

^{1}H NMR ($CDCl_3$): 1.4–1.9 (m, 6H), 2.0–2.2 (m, 1H), 2.4–2.65 (m, 1H), 3.2–4.05 (m, 6H), 4.1–4.2 (m, 2H), 4.45–4.5 (m, 1H), 4.60 (s, 2H), 4.80 (t, 1H), 6.88 (d, 2H), 7.1–7.4 (m, 10H), 7.96 (d, 2H)

1-[4-(2-Benzyloxyethoxy)phenyl]-2-(4-chlorophenyl)-4-(tetrahydro-pyranyloxy)butan-1-one

^{1}H NMR ($CDCl_3$): 1.30–1.90 (m, 6H), 1.95–2.15 and 2.38–2.58 (2m, together 2H), 3.20–4.05 (m, 6H), 4.16 (dist.t., 2H), 4.75–4.85 (m, 1H), 4.61 (s, 2H), 4.80 (t, 1H), 6.88 (d, 2H), 7.13–7.40 (m, 9H), 7.94 (d, 2H)

1,2-Bisphenyl-4-(tetrahydropyranyloxy)butan-1-one

^{1}H NMR ($CDCl_3$): 1.4–1.9 (m, 6H), 2.0–2.2 (m, 1H), 2.4–2.65 (m, 1H), 3.2–3.9 (m, 4H), 4.45–4.5 (m, 1H), 4.85 (t, 1H), 7.1–7.5 (m, 8H), 8.00 (d, 2H)

2-(3-Methoxyphenyl)-1-[4-(2-piperidin-1-ylethoxy)phenyl]-4-(tetrahydro-pyranyloxy)butan-1-one

^{1}H NMR ($CDCl_3$): 1.40–1.90 (m, 13H), 1.95–2.2 (m, 1H), 2.48 (br.t, 4H), 2.75 (t, 2H), 3.20–3.90 (m, 4H) under which 3.76 (s, 3H), 4.11 (t, 2H), 4.49 (m, 1H), 4.77 (m, 1H), 6.73 (dd, 2H), 6.80–6.95 (m, 4H), 7.21 (t, 1H), 7.96 (d, 2H)

2-(2-Methoxyphenyl)-1-[4-(2-piperidin-1-ylethoxy)phenyl]-4-(tetrahydro-pyranyloxy)butan-1-one

^{1}H NMR ($CDCl_3$): 1.30–1.90 (m, 13H), 1.95-2.15 (m, 1H), 2.48 (m, 4H), 2.74 (t, 2H), 3.20–4.00 (m, 4H) under which 3.88 (s, 3H), 4.09 (t, 2H), 4.45–4.55 (m, 1H), 5.22 (m, 1H), 6.73–6.90 (m, 4H) 7.14–7.30 (m, 2H), 7.97 (d, 2H)

e) Grignard reaction with desoxybenzoin derivatives

4-Benzyloxy-2-(4-chlorophenyl)-1-[4-(2-dimethylaminoethoxy)-phenyl]-1-phenylbutan-1-ol

4-Benzyloxy-2-(4-chlorophenyl)-1-[4-(2-dimethylaminoethoxy)phenyl]butan-1-one (9.4 g, 0.021 mol) is added to Grignard reagent prepared from bromobenzene (13.1 g, 0.083 mol) and Mg turnings (2.0 g, 0.083 mol) in dry tetrahydrofuran. The mixture is refluxed for 3 h. Saturated ammonium chloride solution is added to the cooled reaction mixture, the THF layer is separated and the aqueous phase is extracted with toluene. The combined organic phases are washed with water and the solvents are evaporated. The residual product (10.7 g) is used in the next reaction step without further purification.

Using the same method the following compounds are prepared:

4-Benzyloxy-1-[4-(2-dimethylaminoethoxy)phenyl]-2-(4-fluoro-phenyl)-1-phenylbutan-1-ol

is used in the next reaction step without further purification

4-Benzyloxy-2-(4-chlorophenyl)-1-[4-(2-dimethylaminoethoxy)-phenyl]-1-(4-methoxyphenyl)butan-1-ol

is used in the next reaction step without further purification

1-(3-Benzyloxyphenyl)-1-[4-(2-benzyloxyethoxy)phenyl]-2-phenyl-4-(tetrahydropyranyloxy)butan-1-ol

is used in the next reaction step without further purification.

1-[4-(Benzyloxyethoxy)phenyl]-2-(4-chlorophenyl)-1-(4-methoxy-phenyl)-4-(tetrahydropyranyloxy)butan-1-ol

is used in the next reaction step without further purification.

2-(3-Methoxyphenyl)-1-phenyl-1-[4-(2-piperidin-1-ylethoxy)phenyl]-4-(tetrahydropyranyloxy)butan-1-ol

is used in the next reaction step without further purification.

2-(2-Methoxyphenyl)-1-phenyl-1-[4-(2-piperidin-1-ylethoxy)phenyl]-4-(tetra-hydropyranyloxy)butan-1-ol

is used in the next reaction step without further purification.

1-[3-(2-Dimethylaminoethoxy)phenyl]-1,2-diphenyl-4-(tetrahydro-pyranyloxy)butan-1-ol

is used in the next reaction step without further purification.

1-[4-(2-Benzyloxyethylsulfanyl)phenyl]-1,2-diphenyl-4-(tetrahydro-pyranyloxy)butan-1-ol

is used in the next reaction step without further purification.

1-[4-(2-Dimethylaminoethylsulfanyl)phenyl]-1,2-diphenyl-4-(tetrahydro-pyranyloxy)butan-1-ol

is used in the next reaction step without further purification

f) Dehydration of the triarylbutandiol derivatives

(2-{4-[4-Benzyloxy-2-(4-chlorophenyl)-1-phenylbut-1-enyl]-phenoxy}ethyl)dimethylamine

4-Benzyloxy-2-(4-chlorophenyl)-1-[4-(2-dimethylaminoethoxy)phenyl]-1-phenylbutan-1-ol (10.7 g) is dissolved in methanol (70 ml) and concentrated hydrochloric acid is added to make the solution acidic. The mixture is stirred for 4.5 h at room temperature and then at 50 °C for 1 h. The solvent is evaporated and the product is purified by flash chromatography (eluent toluene:triethylamine 24:1). The yield is 5.6 g as a mixture of E- and Z-isomers (1:2).

^{1}H NMR (mixture of Z- and E-isomers, $CDCl_3$): 2.28 and 2.34 (2s, 6H), 2.64 and 2.73 (2t, 2H), 2.78 and 2.83 (2t, 2H), 3.40 and 3.42 (2t, 2H), 3.93 and 4.07 (2t, 2H), 4.36 and 4.38 (2s, 2H), 6.55-7.40 (m, 18H) from which can be identified 6.58 and 6.75 (2d, 4H).

Using the same method the following compounds are prepared:

(2-{4-[4-Benzyloxy-2-(4-fluorophenyl)-1-phenylbut-1-enyl]phenoxy}-ethyl)dimethylamine

^{1}H NMR (mixture of Z- and E-isomers, $CDCl_3$): 2.28 and 2.34 (2s, 6H), 2.65 and 2.74 (2t, 2H), 2.78 and 2.83 (2t, 2H), 3.41 and 3.43 (2t, 2H), 3.93 and

4.07 (2t, 2H), 4.37 and 4.39, (2s, 2H), 6.50-7,40 (m, 18 H) from which can be identified 6.58 and 6.75 (2d, 4H).

(2-{4-[4-Benzyloxy-2-(4-chlorophenyl)-1-(4-methoxyphenyl)but-1-enyl]phenoxy}ethyl)dimethylamine

^{1}H NMR (mixture of Z- and E-isomers, $CDCl_3$): 2.30 and 2.35 (2s, 6H), 2.67 and 2.76 (2t, 2H), 2.81 (t, 2H), 3.41 (t, 2H), 3.69 and 3.81 (2s, 3H), 4.38 (s, 2H), 6.56 and 6.86 (2d, 2H), 6.58 and 6.85 (2d, 2H), 6.75 (d, 2H), 6.76 (d, 2H), 7.0–7.4 (m, 11H)

4-[4-(2-Benzyloxyethoxy)phenyl]-3-(4-chlorophenyl)-4-(4-methoxyphenyl)but-3-en-1-ol

is prepared according to the procedure of the example 1c. The Z- and E-isomers are separated by flash chromatography, eluent toluene:metanol 99:1.

Z-isomer ^{1}H NMR ($CDCl_3$): 2.76 (t, 2H), 3.57 (br.t, 2H), 3.75 (dist.t, 2H), 3.81 (s, 3H), 4.03 (dist.t, 2H), 4.59 (s, 2H), 6.59 (d, 2H), 6.76 (d, 2H), 6.87 (d, 2H), 7.05 (d, 2H), 7.13 (d, 2H), 7.19 (d, 2H), 7.27–7.40 (m, 5H)

E-isomer ^{1}H NMR ($CDCl_3$): 2.76 (t, 2H), 3.58 (br.t, 2H), 3.70 (s, 3H), 3.84 (dist.t, 2H), 4.17 (dist.t, 2H), 4.65 (s, 2H), 6.57 (d, 2H), 6.77 (d, 2H), 6.90 (d, 2H), 7.06 (d, 2H), 7.15 (d, 2H), 7.18 (d, 2H), 7.27–7.40 (m, 5H)

Using the same method the following compounds are prepared.

3-(3-Methoxyphenyl)-4-phenyl-4-[4-(2-piperidin-1-ylethoxy)phenyl]but-3-en-1-ol

Z-isomer: ^{1}H NMR ($CDCl_3$):1.33–1.50 (m, 2H), 1.50–1.65 (m, 4H), 2.45 (br.t., 4H), 2.67 (t, 2H), 2.73 (t, 2H,), 3.58 (t, 2H), 3.65 (s, 3H), 3.96 (t, 2H), 6.55 (d, 2H), 6.63–6.77 (m, 3H), 6.79 (d, 2H), 7.10 (t, 1H), 7.20–7.40 (m, 5H)

E-isomer: ^{1}H NMR ($CDCl_3$): 1.40–1.55 (m, 2H), 1.55–1.70 (m, 4H), 2.51 (br.t., 4H), 2.77 (t, 2H), 2.80 (t, 2H), 3.61 (s, 3H), 3.62 (t, 2H), 3.94 (t, 2H), 6.6–7.25 (m, 13H)

3-(2-Methoxyphenyl)-4-phenyl-4-[4-(2-piperidin-1-ylethoxy)phenyl]but-3-en-1-ol

Z-isomer: ^{1}H NMR ($CDCl_3$):1.33–1.48 (m, 2H), 1.48–1.65 (m, 4H), 2.43 (br.t., 4H), 2.20–2.50 (t, 2H), 2.65 (t, 2H), 3.43–3.60 (t, 2H), 3.62 (s, 3H), 3.93 (t, 2H), 6.52 (d, 2H), 6.70–6.90 (m, 2H) under which 6.82 (d, 2H), 7.05–7.43 (m, 7H)

E-isomer: ^{1}H NMR ($CDCl_3$): 1.38–1.52 (m, 2H), 1.52–1.70 (m, 4H), 2.51 (br.t., 4H), 2.38–2.58 (t, 2H), 2.77 (t, 2H), 3.59 (s, 3H), 3.45–3.65 (m, 2H), 4.10 (t, 2H), 6.6–7.35 (m, 13H)

(E)-4-(3-Benzyloxyphenyl)-4-[4-(2-benzyloxyethoxy)phenyl]-3-phenyl-but-3-en-1-ol

^{1}H NMR ($CDCl_3$): 2.73 (t, 2H), 3.5–3.6 (m, 2H), 3.7–3.76 (m, 2H), 4.0–4.03 (m, 2H), 4.60 (s, 2H), 5.05 (s, 2H), 6.56 (d, 2H), 6.78 (d, 2H), 6.8–6.95 (m, 2H), 7.05–7.35 (m, 17H)

(Z)-4-[4-(2-Benzyloxyethylsulfanyl)phenyl]- 3,4-diphenyl-but-3-en-1-ol

^{1}H NMR ($CDCl_3$): 2.75 (t, 2H), 3.02 (t, 2H), 3.56 (t, 4H), 4.47 (s, 2H), 6.78 (d, 2H), 6.96 (d, 2H), 7.1–7.4 (m, 15H)

(Z)-4-[4-(2-Dimethylaminoethylsulfanyl)phenyl]-3,4-diphenyl-but-3-en-1-ol

MS: EI, m/e 403 (M^+, 1 %), 332 (1 %), 72 (12 %), 58 (100 %)

g) Removal of the protecting benzyl group

3-(4-Chlorophenyl)-4-[4-(2-dimethylaminoethoxy)phenyl]-4-phenylbut-3-en-1-ol

(2-{4-[4-Benzyloxy-2-(4-chlorophenyl)-1-phenylbut-1-enyl]phenoxy}ethyl)dimethylamine (1.1 g, 2.1 mmol) is dissolved in toluene, Zn powder (0.4 g, 6.1 mmol) and acetyl chloride (0.6 g, 7.6 mmol) are added and the mixture is stirred at 40 °C for 3 h. Additional Zn (0.5 g) and acetyl chloride (0.6 g) are added and stirring is continued for another 5 h. Ethyl acetate is added and the precipitate is filtered off. The solvents are evaporated and the residue is dissolved in methanol. The acetate ester of the product is hydrolyzed by making the mixture alkaline with 48 % aqueous sodium hydroxide and stirring the mixture at room temperature for 2 h. Methanol is evaporated, the residue is dissolved in toluene and washed with water. Toluene is evaporated and the isomers of the product are separated by flash chromatography. The yield of the Z-isomer is 0.25 g and of the E-isomer 0.15 g.

Z-isomer: ^{1}H NMR ($CDCl_3$): 2.28 (s, 6H), 2.65 (t, 2H), 2.72 (t, 2H), 3.57 (t, 2H), 3.94 (t, 2H), 6.58 (d, 2H), 6.76 (d, 2H), 7.07 (d, 2H), 7.15 (d, 2H), 7.20–7.40 (m, 5H)

E-isomer: ^{1}H NMR ($CDCl_3$): 2.34 (s, 6H), 2.74 (t, 2H), 2.78 (t, 2H), 3.59 (t, 2H), 4.07 (t, 2H), 6.80–7.30 (m, 13H)

Using the same method the following compounds are prepared:

4-[4-(2-Dimethylaminoethoxy)phenyl]-3-(4-fluorophenyl)-4-phenylbut-3-en-1-ol

Z-isomer: ^{1}H NMR ($CDCl_3$): 2.27 (s, 6H), 2.64 (t, 2H), 2.72 (t, 2H), 3.56 (t, 2H), 3.93 (t, 2H), 6.56 (d, 2H), 6.76 (d, 2H), 6.86 (t, 2H), 7.00–7.40 (m, 7H)

E-isomer: ^{1}H NMR (E-isomer, $CDCl_3$): 2.35 (s, 6H), 2.75 (t, 2H), 2.78 (t, 2H), 3.60 (t, 2H), 4.08 (t, 2H), 6.75–7.40 (m, 13H)

3-(4-Chlorophenyl)-4-[4-(2-dimethylaminoethoxy)phenyl]-4-(4-methoxyphenyl)but-3-en-1-ol

Z-isomer: ^{1}H NMR ($CDCl_3$): 2.28 (s, 6H), 2.65 (t, 2H), 2.75 (t, 2H), 3.57 (t, 2H), 3.81 (s, 3H), 3.94 (t, 2H), 6.58 (d, 2H), 6.75 (d, 2H), 6.87 (d, 2H), 7.05 (d, 2H), 7.13 (d, 2H), 7.19 (d, 2H)

E-isomer: ^{1}H NMR ($CDCl_3$): 2.33 (s, 6H), 2.74 (t, 2H), 2.75 (t, 2H), 3.56 (t, 2H), 3.69 (s, 3H), 4.07 (t, 2H), 6.56 (d, 2H), 6.76 (d, 2H), 6.88 (d, 2H), 7.06 (d, 2H), 7.13 (d, 2H), 7.17 (d, 2H)

h) Conversion of the hydroxyl group to chlorine

(Z)-(2-{4-[4-Chloro-2-(4-chlorophenyl)-1-phenylbut-1-enyl]phenoxy}ethyl)-dimethylamine (No. 23)

(Z)-3-(4-Chlorophenyl)-4-[4-(2-dimethylaminoethoxy)phenyl]-4-phenylbut-3-en-1-ol (0.22 g, 0.5 mmol) is dissolved in toluene. Thionyl chloride (0.2 g, 1.7 mmol) is added and the mixture is refluxed for 45 min. Toluene is partly evaporated and the precipitated hydrochloride salt of the product is filtered. The yield is 0.2 g.

^{1}H NMR (HCl salt, $CDCl_3$): 2.88 and 2.90 (s, together 6H), 2.91 (t, 2H), 3.40 (m, 4H), 4.40 (m, 2H), 6.58 (d, 2H), 6.81 (d, 2H), 7.07 (d, 2H), 7.19 (d, 2H), 7.20–7.50 (m, 5H)

Using the same method the following compounds are prepared:

(E)-(2-{4-[4-Chloro-2-(4-chlorophenyl)-1-phenylbut-1-enyl]phenoxy}ethyl)-dimethylamine (No. 24)

^{1}H NMR (HCl salt, $CDCl_3$): 2.35–3.02 (m, 2H), 2.95 (s, 6H), 3.35-3.55 (m, 4H), 4.46–4.60 (m, 2H), 6.75–7.30 (m, 13H)

(Z)-(2-{4-[4-Chloro-2-(4-fluorophenyl)-1-phenylbut-1-enyl]phenoxy}-ethyl)dimethylamine (No. 25)

^{1}H NMR (HCl salt, $CDCl_3$): 2.88 (s, 6H), 2.94 (t, 2H,), 3.41 (m, 4H), 4.39 (m, 2H), 6.56 (d, 2H), 6.80 (d, 2H), 6.91 (t, 2H), 7.10 (dd, 2H), 7.20–7.40 (m, 5H)

2-{4-[4-Chloro-2-(4-chlorophenyl)-1-(4-methoxyphenyl)but-1-enyl]phenoxy}ethyl)dimethylamine (No. 26 and 27)

Z-isomer (No. 26): ^{1}H NMR (HCl salt, $CDCl_3$ + MeOH-d4): 2.89 (s, 6H), 2.94 (t, 2H), 3.41 (m, 4H), 3.84 (s, 3H), 4.34 (m, 2H), 6.59 (d, 2H), 6.81 (d, 2H), 6.90 (d, 2H), 7.06 (d, 2H), 7.18 (d, 2H), 7.19 (d, 2H)

E-isomer (No. 27): ^{1}H NMR (HCl salt, $CDCl_3$ + MeOH-d4): 2.91 (t, 2H), 2.98 (s, 6H), 3.41 (t, H), 3.54 (m, 2H), 3.71 (s, 3H), 4.45 (m, 2H), 6.59 (d, 2H), 6.77 (d, 2H), 6.94 (d, 2H), 7.06 (d, 2H), 7.17–7.18 (d, 2H), 7.23 (d, 2H)

1-(2-{4-[4-Chloro-2-(3-methoxyphenyl)-1-phenylbut-1-enyl]phenoxy}-ethyl)piperidine (No. 28 and 29)

Z-isomer (No. 28): ^{1}H NMR (HCl salt, MeOH-d4): 1.45–2.10 (m, 6H), 2.92 (t, 2H), 3.06 (dt, 2H), 3.44 (t, 2H), 3.47–3.66 (m, 4H), 3.68 (s, 3H), 4.27 (dist.t., 2H), 6.70–6.85 (m, 5H), 6.92 (d, 2H), 7.15 (dt, 1H), 7.30–7.50 (m, 5H)

E-isomer (No. 29): ^{1}H NMR (HCl salt, MeOH-d4): 1.45–2.15 (m, 6H), 2.96 (t, 2H), 3.12 (dt, 2H), 3.47 (t, 2H), 3.58–3.75 (m, 4H), 3.62 (s, 3H), 4.44 (dist.t., 2H, 6.65–6.83 (m, 3H), 6.90–6.97 (m, 2H), 7.01–7.18 (m, 6H), 7.31 (d, 2H)

1-(2-{4-[4-Chloro-2-(2-methoxyphenyl)-1-phenylbut-1-enyl]phenoxy}-ethyl)piperidine (No. 30 and 31)

Z-isomer (No. 30): ^{1}H NMR (HCl salt, MeOH-d4): 1.50–2.05 (m, 6H), 2.88 (t, 2H), 3.05 (dt, 2H), 3.41 (t, 2H), 3.45–3.65 (m, 4H), 3.86 (s, 3H), 4.25 (dist.t., 2H), 6.65–6.79 (m, 3H), 6.88–7.00 (m, 4H), 7.20 (dt, 1H), 7.30–7.50 (m, 5H)

E-isomer (No. 31): ^{1}H NMR (HCl salt, MeOH-d4): 1.55–2.20 (m, 6H), 2.92 (t, 2H), 3.13 (dt, 2H), 3.43 (t, 2H), 3.58–3.75 (m, 4H), 3.84 (s, 3H), 4.45 (dist.t., 2H), 6.73 (dt, 1H), 6.89–7.30 (m, 7H), 7.08 (d, 2H), 7.18 (dt, 1H), 7.32 (d, 2H)

(Z)-1-[4-(2-Benzyloxyethylsulfanyl)phenyl]- 1,2-diphenyl-4-chloro-but-1-ene

^{1}H NMR ($CDCl_3$): 2.92 (t, 2H), 3.02 (t, 2H), 3.41 (t, 2H), 3.56 (t, 2H), 4.47 (s, 2H), 6.78 (d, 2H), 6.96 (d, 2H), 7.10–7.40 (m, 15H)

(Z)-1-[4-(2-Dimethylaminoethylsulfanyl)phenyl]-1,2-diphenyl-4-chloro-but-1-ene (No. 32)

^{1}H NMR ($CDCl_3$): 2.28 (s, 6H), 2.46 (dist. t, 2H), 2.85–2.95 (m, 4H), 3.41 (dist. t, 2H), 6.79 (d, 2H), 6.96 (d, 2H), 7.00–7.40 (m, 10H)

1-[4-(2-Benzyloxyethoxy)phenyl]-4-chloro-2-(4-chlorophenyl)-1-(4-methoxy-phenyl)but-1-ene

Z-isomer, ^{1}H NMR ($CDCl_3$): 2.93 (t, 2H), 3.41 (t, 2H), 3.83 (s, 2H), 3.76 (dist.t, 2H), 4.04 (dist.t, 2H), 4.59 (s, 2H), 6.59 (d, 2H), 6.77 (d, 2H), 6.87 (d, 2H), 7.05 (d, 2H), 7.15 (d, 2H), 7.19 (d, 2H), 7.27–7.40 (m, 5H)

E-isomer ^{1}H NMR ($CDCl_3$): 2.93 (t, 2H), 3.41 (t, 2H), 3.70 (s, 3H), 3.85 (dist.t, 2H), 4.18 (dist.t, 2H), 4.65 (s, 2H), 6.57 (d, 2H), 6.79 (d, 2H), 6.92 (2H), 7.06 (d, 2H), 7.16 (d, 2H), 7.18 (d, 2H), 7.27–7.40 (m, 5H)

(E)-1-(3-Benzyloxyphenyl)-1-[4-(2-benzyloxyethoxy)phenyl]-4-chloro-3-phenyl-but-1-ene

The compound is prepared by using the method described in the examples 1d using Ph_3P and CCl_4 as reagents.

^{1}H NMR ($CDCl_3$): 2.93 (t, 2H), 3.40 (t, 2H), 3.71–3.76 (m, 2H), 3.98–4.05 (m, 2H), 4.58 (s, 2H), 5.06 (s, 2H), 6.60 (d, 2H), 6.78 (d, 2H), 6.85–7.50 (m, 19H)

(Z)-{2-[3-(4-Chloro-1,2-diphenylbut-1-enyl)phenoxy]ethyl}dimethylamine (No. 33)

1-[3-(2-Dimethylaminoethoxy)phenyl]-1,2-diphenyl-4-(tetrahydropyranyloxy)butan-1-ol (0.93 g, 1,9 mmol) is dissolved in toluene (10 ml). Triethylamine (1.9 mmol) is added to the solution and the mixture is

cooled to –10 °C. Thionyl chloride (5.8 mmol) is added to the mixture at –10 – ±0 °C. The mixture was stirred for 1 hour at 0–5 °C, warmed up to 80 °C and stirred at this temperature for 3 hours. Solvent was evaporated, the residue was dissolved to toluene, washed with 2 N NaOH and with water. The Z-isomer of the product was crystallized from ethyl acetate as HCl salt. Yield 0.15 g

^{1}H NMR (HCl salt, $CDCl_3$): 2.79 (s, 6H), 2.94 (t, 2H), 3.20–3.29 (m, 2H), 3.42 (t, 2H), 4.12–4.20 (m, 2H), 6.40 (s, 1H), 6.51–6.62 (m, 2H), 6.98 (t, 1H), 7.10–7.45 (m, 10H)

i) Removal of the protecting groups

(E)-3-{4-Chloro-1-[4-(2-hydroxyethoxy)phenyl]-2-phenyl-but-1-enyl}-phenol (No. 34)

(E)-4-(3-Benzyloxyphenyl)-4-[4-(2-benzyloxyethoxy)phenyl]-4-chloro-3-phenyl-but-1-ene (1.95 g, 3.39 mmol) is hydrogenated in ethanol-ethyl acetate (5 ml:20 ml) containing triethylamine (3.4 mmol) and 10 % palladium on carbon (0.195 g) as a catalyst. The catalyst is filtered off and the solvent is evaporated. The product is purified with flash chromatography and crystallized from toluene-methanol (9:1). Yield 0.23 g.

^{1}H NMR ($CDCl_3$ + MeOH-d4): 2.95 (t, 2H), 3.42 (t, 2H), 3.8–4.0 (m, 4H), 6.56 (d, 2H), 6.75–6.82 (m, 4H), 7.10–7.25 (m, 7H)

Using the same method the following compound included in the invention is prepared:

(Z)-3-[4-(4-Chloro-1,2-diphenylbut-1-enyl)phenoxy]propan-1-ol (No. 35)

^{1}H NMR ($CDCl_3$): 1.96 (quint., 2H), 2.92 (t, 2H), 3.42 (t, 2H), 3.80 (q, 2H), 3.98 (t, 2H), 6.55 (d, 2H), 6.78 (d, 2H), 7.11–7.40 (m, 10H)

(Z)-2-[4-(4-Chloro-1,2-diphenyl-but-1-enyl)-phenylsulfanyl]ethanol (No. 36)

is prepared according to the procedure of the example 2g.

^{1}H NMR ($CDCl_3$): 2.93 (t, 2H), 3.00 (t, 2H), 3.41 (t, 2H), 3.64 (t, 2H), 6.81 (d, 2H), 7.01 (d, 2H), 7.10–7.40 (m, 10H)

Using the same method the following compound included in the invention is prepared.

(Z)-2-{4-[4-Chloro-2-(4-chlorophenyl)-1-(4-methoxyphenyl)but-1-enyl]-phenoxy}ethanol (No. 37)

^{1}H NMR ($CDCl_3$): 2.94 (t, 2H), 3.41 (t, 2H), 3.83 (s, 3H), 3.85–4.00 (m, 4H), 6.59 (d, 2H), 6.78 (d, 2H), 6.90 (d, 2H), 7.06 (d, 2H), 7.16 (d, 2H), 7.19 (d, 2H)

Example 5

a) 1-[4-(2-Chloroethoxy)phenyl]-2-(2-chlorophenyl)ethanone

1-[4-(2-Chloroethoxy)phenyl]-2-(2-chlorophenyl)ethanone is prepared according to the method described in the example 4a using 2-chloroethoxybenzene and 2-chlorophenylacetic acid as starting materials.

^{1}H NMR ($CDCl_3$): 3.85 (t, 2H), 4.30 (t, 2H), 4.39 (s, 2H), 6.98 (d, 2H), 7.22–7.26 (m, 3H), 7.39–7.50 (m, 1H), 8.04 (d, 2H)

Using the same method the following compound is prepared:

1-[4-(2-Chloroethoxy)phenyl]-2-phenylethanone

^{1}H NMR ($CDCl_3$): 3.83 (t, 2H), 4.24 (s, 2H), 4.28 (t, 2H), 6.94 (d, 2H), 7.2–7.4 (m, 5H), 8.00 (d, 2H)

b) 2-(2-Chlorophenyl)-1-[4-(2-piperidinylethoxy)phenyl]ethanone

The mixture of 1-[4-(2-chloroethoxy)phenyl]-2-(2-chlorophenyl)ethanone (4 g, 13 mmol) and piperidine (5.8 g, 68 mmol) in 80% aqueous acetone (50 ml) is refluxed for 12 h. Additional portions of 0.3 g of piperidine are added three times in 4 h intervals to the mixture. The solvents are evaporated. Diethyl ether is added and the precipitated piperidine hydrochloride is filtered off. Diethyl ether is evaporated and the residual product is purified by flash chromatography (eluent toluene:triethylamine 9:1). The yield is 4.1 g, 89 %.

^{1}H NMR ($CDCl_3$): 1.38–1.56 (m, 2H), 1.56-1.68 (m, 4H), 2.45–2.62 (m, 4H), 2.79 (t, 2H), 4.17 (t, 2H), 4.38 (s, 2H), 6.96 (d, 2H), 7.19–7.25 and 3.37–7.44 (2m, together 4H), 8.01 (d, 2H)

1-[4-(2-Imidazol-1-yl-ethoxy)phenyl]-2-phenyl ethanone

is prepared from 1-[4-(2-chloroethoxy)phenyl]-2-phenylethanone and imidazole in DMF using sodium hydride as a base according to the procedure described in the example 1a.

^{1}H NMR ($CDCl_3$): 4.22 (s, 2H), 4.20–4.37 (m, 4H), 6.88 (d, 2H), 7.03 (s, 1H), 7.07 (s, 1H), 7.20–7.37 (m, 5H), 7.60 (s, 1H), 7.97 (d, 2H)

c) 2-(2-Chlorophenyl-1-[4-(2-piperidinylethoxy)phenyl]-4-(tetrahydro-pyranyloxy)butan-1-one

2-(2-Chlorophenyl-1-[4-(2-piperidinylethoxy)phenyl]-4-(tetrahydropyranyl-oxy)butan-1-one is prepared by PTC reaction according to the method described in the example 4d using 2-(2-chlorophenyl)-1-[4-(2-piperidinylethoxy)phenyl]-ethanone (1.5 g, 4.2 mmol) and 2-tetrahydropyranyloxy-1-iodoethane (1.3 g, 5.1 mmol) as the starting materials. The product (1.6 g) is used for the following reaction step without further purification.

^{1}H NMR ($CDCl_3$): from the complex spectrum can be identified 2.40–2.60 (m, 4H), 2.75 (t, 2H), 4.12 (t, 2H), 4.50–4.62 (m, 1H), 5.24–5.36 (m, 1H), 6.87 (d, 2H), 7.10–7.25 and 3.37–7.44 (2m, together 4H), 7.98 (d, 2H)

Using the same method the following compound is prepared.

1-[4-(2-Imidazol-1-yl-ethoxy)phenyl]-2-phenyl-4-(tetrahydro-pyranyloxy)butan-1-one

^{1}H NMR ($CDCl_3$): 1.4–1.9 (m, 6H), 1.95–2.2 (m, 1H), 2.4–2.60 (m, 1H), 3.2–3.9 (m, 4H), 4.2–4.37 (m, 4H), 4.45–4.55 (m, 1H), 4.79 (dt, 1H), 6.80 (dd, 2H), 6.99 (s, 1H), 7.05 (s, 1H), 7.15–7.3 (m, 5H), 7.55 (s, 1H), 7.95 (d, 2H)

d) 2-(2-Chlorophenyl-1-phenyl-1-[4-(2-piperidinylethoxy)phenyl]-4-(tetrahydropyranyloxy)butan-1-ol

is prepared according to the procedure described in the example 4e. The product is used in the following reaction step without further purification.

Using the same method the following compounds are prepared:

1-[4-(2-Imidazol-1-yl-ethoxy)phenyl]-2-phenyl-4-(tetrahydro-pyranyloxy)-1-[3-(tetrahydro-pyranyloxy)phenyl]-butan-1-ol

The compound is used in the next reaction step without further purification.

e) 1-(2-{4-[-(2-Chlorophenyl)-4-phenyl-4-[4-(2-piperidin-1-ylethoxy)-phenyl]but-3-en-1-ol

2-(2-Chlorophenyl-1-phenyl-1-[4-(2-piperidinylethoxy)phenyl]-4-(tetrahydro-pyranyloxy)butan-1-ol is dehydrated according to the procedure described in the example 1c. The Z-isomer of the product is purified by flash chromatography (eluent toluene-triethylamine 13:1)

Z-isomer: ^{1}H NMR ($CDCl_3$): 1.35–1.48 (m, 2H), 1.48–1.68 (m, 4H), 2.38–2.48 (m, 4H), 2.66 (t, 2H), 2.58-2.87 (m, 2H), 3.47–3.67 (m, 2H), 3.94 (t, 2H), 6.54 (d, 2H), 6.84 (d, 2H), 7.07–7.41 (m, 9H)

Using the same method the following compound is prepared.

3-{4-Hydroxy-1-[4-(2-imidazol-1-yl-ethoxy)phenyl]-2-phenyl-but-1-enyl}-phenol

E-isomer: ^{1}H NMR ($CDCl_3$+MeOH-d4): 2.83 (t, 2H), 3.60 (t, 2H), 4.11 (dist. t, 2H), 4.20 (t, 2H), 6.48 (d, 2H), 6.76 (d, 2H), 6.66–6.9 (m, 4H), 6.92 (s, 1H), 6.98 (s, 1H), 7.08–7.32 (m, 5H), 7.36 (s, 1H)

Z-isomer: ^{1}H NMR ($CDCl_3$+MeOH-d4): 2.73 (t, 2H), 3.54 (t, 2H), 4.23–4.4 (m, 4H), 6.35–7.23 (m, 15H), 7.55 (s, 1H)

f) (Z)-1-(2-{4-[4-Chloro-2-(2-chlorophenyl)-1-phenylbut-1-enyl]phenoxy}-ethyl)piperidine (No. 38)

is prepared according to the procedure described in the example 1d.

^{1}H NMR ($CDCl_3$): 1.33–1.49 (m, 2H), 1.49–1.68 (m, 4H), 2.40–2.50 (m, 4H), 2.67 (t, 2H), 2.80–3.50 (m, 2H), 3.25–3.56 (m, 2H), 3.95 (t, 2H), 6.54 (d, 2H), 6.85 (d, 2H), 7.06–7.43 (m, 9H)

Using the same method the following compound included in the invention is prepared.

3-{4-Chloro-1-[4-(2-imidazol-1-yl-ethoxy)phenyl]-2-phenyl-but-1-enyl}-phenol (No. 39 and 40)

E-isomer (No. 39): ^{1}H NMR ($CDCl_3$): 2.94 (t, 2H), 3.41 (t, 2H), 4.07 (dist. t, 2H), 4.25 (t, 2H), 6.50 (d, 2H), 6.79 (d, 2H), 6.70–6.81 (m, 2H), 6.98 (s, 2H), 7.10–7.24 (m, 7H), 7.51 (s, 1H)

Z-isomer (No. 40): ^{1}H NMR ($CDCl_3$+MeOH-d4, HCl-salt): 2.90 (dist.t, 2H), 3.40 (dist.t, 2H), 4.33 (dist. t, 2H), 4.65 (dist.t, 2H), 6.35–7.25 (m, 13H), 7.38 (s, 1H), 7.48 (s, 1H), 9.20 (s, 1H)

Example 6

a) (4-Amino-phenyl)phenyl-methanone

4-Nitrobenzophenone (5.0 g, 0.022 mol) is dissolved in ethanol-dichloromethane (40 ml : 30 ml) and hydrogenated at room temperature with 10 % palladium on carbon (0.5 g) as a catalyst. The catalyst is filtered off

and the filtrate is evaporated to dryness. The product is used in the next reaction step without further purification. Yield 5.2 g.

^{1}H NMR ($CDCl_3$): 6.67 (d, 2H), 7.4–7.6 (m, 3H), 7.7–7.6 (m, 4H)

b) McMurry reaction

4-(4-Chloro-1,2-diphenyl-but-1-enyl)phenylamine

Zinc (10.0 g, 0.154 mol) and tetrahydrofuran (THF) (120 ml) is added to the reaction vessel and cooled to –10 °C. To the mixture is added dropwise titan tetrachloride (14.4 g, 0.076 mol) at about –10 °C. After the addition is completed the mixture is refluxed for two hours. Then it is cooled to 40 °C and (4-Amino-phenyl)phenyl-methanone (5.1 g, 0.0258 mol) and 3-chloropropiophenone (4.36 g, 0.0258 mol) are dissolved in THF (50 ml) and added to the mixture. Refluxing is continued for additional 3.5 hours. The cooled reaction mixture is poured in aqueous potassium carbonate solution (14 g K_2CO_3 + 140 ml water) and allowed to stand over night. The mixture is filtered and the precipitate is washed three times with THF. The filtrate is evaporated to dryness. The residue is dissolved in ethyl acetate and washed with water. Yield 9.6 g Z-isomer being the only isomer.

Z-isomer: ^{1}H NMR ($CDCl_3$): 2.90 (t, 2H), 3.41 (t, 2H), 6.32 (d, 2H), 6.64 (d, 2H), 7.0–7.4 (m, 10H)

Using the same method the following compound included in the invention is prepared

N-[4-(4-Chloro-1,2-diphenyl-but-1-enyl)-phenyl]-N',N'-dimethylethane-1,2-diamine (No. 47)

starting from [4-(2-dimethylaminoethylamino)phenyl]phenyl methanone (preparation described in US patent no. 5,693,674) and 3-chloropropiophenone.

Z-isomer: ^{1}H NMR (as HCl-salt, MeOH-d4): 2.95 (s, 6H), 2.99 (t, 2H), 3.44 (t, 2H), 3.47 (t, 2H), 3.68 (t, 2H), 6.90–7.10 (m, 4H), 7.15–7.40 (m, 10H)

c) (Z)-[4-(4-Chloro-1,2-diphenyl-but-1-enyl)phenylamino]acetic acid ethyl ester

(Z)-4-(4-Chloro-1,2-diphenyl-but-1-enyl)phenylamine (2.0 g, 5.99 mmol), ethanol (30 ml), ethyl bromoacetate (2.5 g, 15 mmol) and sodium acetate (2.4 g, 17.9 mmol) are added to the reaction vessel and refluxed for three hours. Then the solvent is evaporated and the residue is dissolved in water and ethyl acetate. Ethyl acetate phase is dried and evaporated to dryness. Yield 2.9 g.

^{1}H NMR ($CDCl_3$): 1.26 (t, 3H), 2.90 (t, 2H), 3.41 (t, 2H), 4.20 (q, 2H), 6.25 (d, 2H), 6.68 (d, 2H), 7.10–7.40 (m, 10H)

d) (Z)-2-[4-(4-Chloro-1,2-diphenyl-but-1-enyl)phenylamino]ethanol (No. 41)

(Z)-[4-(4-Chloro-1,2-diphenyl-but-1-enyl)phenylamino]acetic acid ethyl ester (2.9 g, 6.9 mmol) is dissolved in tetrahydrofuran and lithium aluminum hydride (0.34 g, 8.97 mmol) is added in small portions during fifteen minutes. The mixture is stirred at room temperature for two hours. Then the solvent is evaporated to dryness and the residue is dissolved in ethyl acetate and washed with water. Ethyl acetate phase is evaporated to dryness and the product is purified by flash chromatography with toluene:methanol:triethylamine solution (10:0.3:0.3) as an eluent. Yield 0.47 g.

^{1}H NMR ($CDCl_3$): 2.89 (t, 2H), 3.17 (t, 2H), 3.41 (t, 2H), 3.73 (t, 2H), 6.29 (d, 2H), 6.67 (d, 2H), 7.10–7.40 (m, 10H)

Example 7

a) 4-{2-[4-(2-Benzyloxyethoxy)phenyl]-1-(2-chloroethyl)-2-phenylvinyl}phenol

is prepared according to the method of example 6b using [(4-benzyloxyethoxy)phenyl]phenylmethanone and 3-chloro-1-(4-hydroxyphenyl)propan-1-one as starting materials. The product is mixture of Z- and E-isomers.

^{1}H NMR ($CDCl_3$): 2.88 and 2.93 (2t, 2H), 3.42 and 3.43 (2t, 2H), 3.74 and 3.84 (2dist.t, 2H), 4.01 and 4.16 (2dist.t, 2H), 4.58 and 4.65 (2s, 2H), 6.55–7.40 (m, 18H)

b) 4-{1-(2-Chloroethyl)-2-[4-(2-hydroxyethoxy)phenyl]-2-phenylvinyl}phenol (No. 42 and 43)

is prepared according to the procedure of the example 1e. The isomers are purified by flash chromatography (eluent dichloromethane-methanol-triethylamine 98:2:1)

Z-isomer (No. 42): ^{1}H NMR ($CDCl_3$): 2.87 (t, 2H), 3.43 (t, 2H), 3.83–3.90 (m, 2H), 3.90–3.97 (m, 2H), 6.56 (d, 2H), 6.66 (d, 2H), 6.80 (d, 2H), 6.96 (d, 2H), 7.20–7.40 (m, 5H)

E-isomer (No. 43): ^{1}H NMR ($CDCl_3$): 2.92 (t, 2H), 3.38 (t, 2H), 3.90–4.02 (m, 2H), 4.03–4.14 (m, 2H), 6.63 (d, 2H), 6.89 (d, 2H), 6.95 (d, 2H), 7.20 (d, 2H), 6.85–7.17 (m, 5H)

Example 8

{2-[4-(4-Chloro-1,2-diphenylbut-1-enyl)phenoxy]ethyl}methylprop-2-ynylamine (No. 44)

is prepared according to example 1 a starting from Z-4-chloro-1,2-diphenyl-1[4-[2-(N-methylamino)ethoxy]-phenyl]-1-butene (preparation described in US patent no 5,491173) and propargyl bromide.

^{1}H NMR (citrate salt, MeOH-d4): 2.74 (s, 3H), 2.82 and 2.86 (2s, 4H), 2.93 (t, 2H), 3.06 (t, 1H), 3.29 (dist. t, 2H), 3.44 (t, 2H), 3.85 (d, 2H), 4.16 (dist. t, 2H), 6.68 (d, 2H), 6.86 (d, 2H), 7.15–7.47 (m, 10H)

Example 9

a) (Z)-[4-(4-Hydroxy-1,2-diphenylbut-1-enyl)phenyloxy]acetic acid ethyl ester

is prepared from (Z)-(4-hydroxy-1,2-diphenylbut-1-enyl)phenol (preparation described in US patent no. 4.996.225) and ethyl bromoacetate according to the procedure described in the example 1a using NaH as a base.

^{1}H NMR ($CDCl_3$): 1.25 (t, 3H), 2.74 (t, 2H), 3.57 (t, 2H), 4.23 (q, 2H), 4.47 (s, 2H), 6.56 (d, 2H), 6.79 (d, 2H), 7.10–7.45 (m, 10H)

(Z)-2-[4-(4-Hydroxy-1,2-diphenylbut-1-enyl)phenoxy]butyric acid ethyl ester

is prepared according to the same procedure using ethyl 2-bromobutyrate as a alkylating reagent.

^{1}H NMR (MeOH-d_4): 0.98 (t, 3H), 1.17 (t, 3H), 1.86 (m, 2H), 2.70 (t, 2H), 3.47 (t, 2H), 4.12 (m, 2H), 4.50 (dd, 1H), 6.50 (d, 2H), 6.76 (d, 2H), 7.0–7.4 (m, 10H)

b) (Z)-[4-(4-Chloro-1,2-diphenylbut-1-enyl]phenoxy)acetic acid ethyl ester

is prepared according to procedure described in the example 1d using Ph_3P and CCl_4 as reagents.

^{1}H NMR ($CDCl_3$): 1.25 (t, 3H), 2.92 (t, 2H), 3.41 (t, 2H), 4.23 (q, 2H), 4.50 (s, 2H), 6.55 (d, 2H), 6.80 (d, 2H), 7.10–7.45 (m, 10H)

Using the same method the following compound is prepared

(Z)-2-[4-(4-Chloro-1,2-diphenylbut-1-enyl)phenoxy]butyric acid ethyl ester

^{1}H NMR (MeOH-d_4): 1.01 (t, 3H), 1.16 (t, 3H), 1.89 (m, 2H), 2.91 (t, 2H), 3.40 (t, 2H), 4.15 (m, 2H), 4.40 (dd, 1H), 6.52 (d, 2H), 6.76 (d, 2H), 7.0–7.4 (m, 10H)

c) (Z)-3-[4-(4-Chloro-1,2-diphenylbut-1-enyl)phenoxymethyl]pentan-3-ol (No. 45)

Grignard reagent is prepared from Mg turnings (0.29 g, 12 mmol) and bromoethane (1.25 g, 12 mmol) in tetrahydrofuran (4 ml). (Z)-[4-(4-Chloro-1,2-diphenylbut-1-enyl]phenoxy)acetic acid ethyl ester (1.0 g, 23 mmol, from example 9b) in tetrahydrofuran (11 ml) is added in room temperature and the reaction mixture is refluxed for 2 h. Saturated ammonium chloride is added

and tetrahydrofuran is evaporated. The product is extracted into ethyl acetate. The organic layer is dried and evaporated to dryness. The yield is 1.0 g .

^{1}H NMR ($CDCl_3$): 0.87 (t, 6H), 1.58 (q, 4H), 2.92 (t, 2H), 3.42 (t, 2H), 3.68 (s, 2H), 6.56 (d, 2H), 6.78 (d, 2H), 7.10–7.45 (m, 10H)

Example 10

(Z)-2-[4-(4-Chloro-1,2-diphenylbut-1-enyl)phenoxy]butan-1-ol (No. 46)

Z-2-[4-(4-Chloro-1,2-diphenylbut-1-enyl)phenoxy]butyric acid ethyl ester (0.98 g, 2.2 mmol) is reduced by lithium aluminum hydride (0.041 g, 1.1 mmol) in tetrahydrofuran. Ice-water is added and tetrahydrofuran is evaporated. The product is extracted into ethyl acetate, dried and the solvent is evaporated. Yield 0.55 g.

^{1}H NMR ($CDCl_3$): 0.89 (t, 3H), 1.54–1.70 (m, 2H), 2.91 (t, 2H), 3.58-3.76 (m, 2H), 4.10–4.20 (m, 1H), 6.57 (d, 2H), 6.77 (d, 2H), 7.10–7.40 (m, 10H)

Example 11

E-3- (4-Chloro-1-{4-[2-(2-hydroxyethoxy)ethoxy]phenyl}-2-phenylbut-1-enyl)phenol

a) 1-{4-[2-(2-Benzyloxyethoxy)ethoxy]phenyl}-2-phenyl ethanone

is prepared according to example 4c starting from 1-(4-hydroxyphenyl)-2-phenyl ethanone (prepared according examples 4 a-b)(10.0 g, 47.1 mmol) and 2-(2-benzyloxyethoxy)ethyl chloride (11.0 g, 51.8 mmol). The product was triturated three times with warm heptane to remove byproducts. Yield 9.6 g, 52 %.

^{1}H NMR ($CDCl_3$): 3.60-3.79 (m, 4H), 3.85 (dist. t, 2H), 4.16 (dist. t, 2H), 4.20 (s, 2H), 4.56 (s, 2H), 6.92 (d, 2H), 7.20–7.41 (m, 10H), 7.96 (d, 2H)

b) 1-{4-[2-(2-Benzyloxyethoxy)ethoxy]phenyl}-2-phenyl-4-(tetrahydropyran-2-yloxy)butan-1-one

is prepared by using the method described in the example 4d starting from 1-{4-[2-(2-benzyloxyethoxy)ethoxy]phenyl}-2-phenylethanone (8.4g, 21.5 mmol) and 2-(tetrahydropyran-2-yloxy)ethyl iodide (6.6 g, 25.8 mmol). The product (11.7 g) is used in the next reaction step without further purification.

^{1}H NMR ($CDCl_3$): 1.40–1.95 (m, 6H), 2.00–2.20 and 2.40–2.60 (2m, together 2H), 3.60–3.80 (m, 8H), 3.83 (dist.t, 2H), 4.13 (dist.t, 2H), 4.45–4.55 (m, 1H), 4.55 (s, 2H), 4.80 (t, 1H), 6.86 (d, 2H), 7.14–7.39 (m, 10H), 7.96 (d, 2H)

c) 1-{4-[2-(2-Benzyloxyethoxy)ethoxy]phenyl}-2-phenyl-4-(tetrahydropyran-2-yloxy)-1-[3-(tetrahydropyran-2-yloxy)phenyl]butan-1-ol

is prepared by using the method described in the example 4e starting from 1-{4-[2-(2-benzyloxyethoxy)ethoxy]phenyl}-2-phenyl-4-(tetrahydropyran-2-yloxy)butan-1-one (10 g, 19.2 mmol) and 3-(tetrahydropyran-2-yloxy)phenyl bromide (9.8 g, 38 mmol). The product is purified by flash chromatography with toluene-methanol (50:1) as eluent. Yield 5.7 g, 43 %.

^{1}H NMR ($CDCl_3$): 1.40–2.20 (m, 10H), 3.5-4.1 (m, 14H), 4.30-4.50 (2m, 1H), 4.52 (s, 1H), 4.53 (s, 1H), 6.60 (d, 2H), 6.90–7.40 (m, 16H).

d)Z,E-3-(1-{4-[2-(2-Benzyloxyethoxy)ethoxy]phenyl}-4-hydroxy-2-phenylbut-1-enyl)phenol

is prepared from 1-{4-[2-(2-benzyloxyethoxy)ethoxy]phenyl}-2-phenyl-4-(tetrahydropyran-2-yloxy)-1-[3-(tetrahydropyran-2-yloxy)phenyl]butan-1-ol

(5.7 g, 8.2 mmol) by using the method described in the example 1c except that toluene is used instead of acetic anhydride (30 ml) and triethylamine (0.91 g, 0.9 mmol) is added. The product (3.8 g) is used in the next reaction step without further purification.

^{1}H NMR ($CDCl_3$): 2.78 (t, 2H), 3.55-4.20 (m, 10H), 4.55 and 4.58 (2s, 2H), 6.56 (d, 2H), 6.73-6.93 (m, 3H), 7.1–7.4 (m, 13H).

e) Z,E-3- (1-{4-[2-(2-Benzyloxyethoxy)ethoxy]phenyl}-4-chloro-2-phenylbut-1-enyl)phenol

is prepared from Z,E-3- (1-{4-[2-(2-benzyloxyethoxy)ethoxy]phenyl}-4-hydroxy-2-phenylbut-1-enyl)phenol (3.8 g, 7.4 mmol) by using the method described in example 4h except that triethylamine (1.64 g, 16.2 mmol) is added to the reaction mixture. The product is purified by flash chromatography. Yield 2.5 g.

^{1}H NMR ($CDCl_3$): 2.92 (t, 2H), 3.40 (t, 2H), 3.58-4.17 (m, 8H) 4.53 and 4.57 (2s, 2H), 6.53 (d, 2H), 6.71-6.9 (m, 6H), 7.1–7.4 (m, 10H).

f) E-3- (4-Chloro-1-{4-[2-(2-hydroxyethoxy)ethoxy]phenyl}-2-phenylbut-1-enyl)phenol

Z,E-3-(1-{4-[2-(2-Benzyloxyethoxy)ethoxy]phenyl}-4-chloro-2-phenylbut-1-enyl)phenol (2.0 g, 3.78 mmol) is dissolved in ethyl acetate (30 ml). Zn (0.062 g, 0.95 mmol) and acetyl chloride (0.74 g, 9.5 mmol) are added under nitrogen atmosphere. The mixture is stirred at 50 C° for 3 h. The mixture is filtered and the solvent is evaporated. The residue is dissolved in 80 % aqueous methanol containing 3% of sodium hydroxide. The mixture is stirred at room temperature for 2 h and methanol is evaporated. Water (5 ml) is added and the product is extracted into ethyl acetate (10 ml). The mixture is dried and the solvent is evaporated. The product is purified first by flash

chromatography (eluent toluene:methanol 9:1) and then crystallized from toluene and recrystallized from toluene-acetone. Yield 0.15 g.

^{1}H NMR ($CDCl_3$): 2.94 (t, 2H), 3.41 (t, 2H), 3.59-3.63 (m, 2H), 3.67-3.72 (m, 2H), 3.78 (dist.t, 2H), 4.01 (dist.t, 2H), 6.56 (d, 2H), 6.78 (d, 2H), 6.70-6.90 (m, 3H), 7.1–7.3 (m, 6H).

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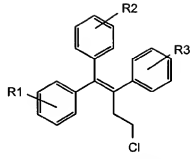
CLAIMS

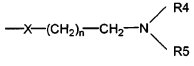
1. A compound of the formula:



(I)

wherein R1 and R2, which are the same or different, are

a) H, halogen, OCH_3, OH; or

b) 

where X is O, NH or S; and n is an integer from 1 to 4; and

R4 and R5, which are the same or different, are a 1 to 4 carbon alkyl, H, $-CH_2C{\equiv}CH$ or $-CH_2CH_2OH$; or

R4 and R5 form an N-containing five- or six-membered ring or heteroaromatic ring; or

c) $-Y-(CH_2)_nCH_2-O-R6$

where Y is O, NH or S and n is an integer from 1 to 4; and

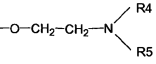
R6 is H, $-CH_2CH_2OH$, or $-CH_2CH_2Cl$; or

d) 2,3-dihydroxypropoxy, 2-methylsulfamylethoxy, 2-chloroethoxy, 1-ethyl-2-hydroxyethoxy, 2,2-diethyl-2-hydroxyethoxy or carboxymethoxy; and

R3 is H, halogen, OH or $-OCH_3$; and

their non-toxic pharmaceutically acceptable salts and esters and mixtures thereof,

provided that

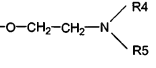
a) when R2 is  in the 4-position of the phenyl

where R4 and R5

i) are the same, either methyl or ethyl; or

ii) form an N-containing five-membered ring ;

then R1 and R3 cannot simultaneously be H; and

b) when R2 is  in the 4-position of the phenyl

where R4 and R5, which are the same or different, are methyl or H; or

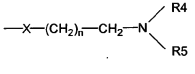
when R2 is -O-CH_2CH_2-OH or -O-CH_2COOH in the 4-position of the phenyl,

then R1 and R3, cannot simultaneously be H, or OH in the 4-position of the phenyl; and

if R1 is OH in the 4-position of the phenyl, R3 cannot be H.

2. A triphenylethylene according to claim 1, wherein R1 and R2 , which are the same or different are

a) H, halogen, OCH_3, OH; or

b) 

where X is O, NH or S; and n is an integer from 1 to 4; and R4 and R5, which are the same or different, are a 1 to 4 carbon alkyl, H, $-CH_2C{\equiv}CH$ or $-CH_2CH_2OH$; or R4 and R5 form an N-containing five- or six-membered ring or heteroaromatic ring.

3. A triphenylethylene according to claim 2 where X is O.

4. A triphenylethylene according to claim 3 where n is 1, and R4 and R5 are methyl or form a piperidine or imidazole ring.

5. A triphenylethylene according to claim 2 where X is S.

6. A triphenylethylene according to claim 2 where X is NH.

7. A compound according to claim 4, which is selected from the group consisting of

(2-{4-[4-chloro-1-(4-fluorophenyl)-2-phenylbut-1-enyl]phenoxy}ethyl)-dimethylamine,

(2-{4-[4-chloro-1-(4-chlorophenyl)-2-phenylbut-1-enyl]phenoxy}ethyl)-dimethylamine,

(2-{4-[4-chloro-1,2-bis(4-chlorophenyl)but-1-enyl]phenoxy}ethyl)-dimethylamine,

(2-{4-[4-chloro-2-(4-fluorophenyl)-1-phenylbut-1-enyl]phenoxy}ethyl)-dimethylamine,

(2-{4-[4-chloro-2-(4-chlorophenyl)-1-phenylbut-1-enyl]phenoxy}ethyl)-dimethylamine,

(2-{4-[4-chloro-2-(4-chlorophenyl)-1-(4-methoxyphenyl)but-1-enyl]phenoxy}ethyl)dimethylamine,

{2-[3-(4-chloro-1,2-diphenylbut-1-enyl)phenoxy]ethyl}dimethylamine,

1-{2-[4-(4-chloro-1,2-diphenyl-but-1-enyl)phenoxy]ethyl}-1H-imidazole,

{2-[4-(4-chloro-1,2-diphenylbut-1-enyl)phenoxy]ethyl}methylprop-2-ynylamine,

2-({2-[4-(4-chloro-1,2-diphenyl-but-1-enyl)phenoxy]ethyl}methylamino)-ethanol,

3-{4-chloro-1-[4-(2-imidazol-1-yl-ethoxy)phenyl]-2-phenyl-but-1-enyl}-phenol,

1-(2-{4-[4-chloro-2-(2-chlorophenyl)-1-phenylbut-1-enyl]phenoxy}ethyl)-piperidine,

1-(2-{4-[4-chloro-2-(3-methoxyphenyl)-1-phenylbut-1-enyl]phenoxy}ethyl)-piperidine, and

1-(2-{4-[4-chloro-2-(2-methoxyphenyl)-1-phenylbut-1-enyl]phenoxy}ethyl)-piperidine.

8. A compound according to claim 5, which is

1-[4-(2-dimethylaminoethylsulfanyl)phenyl]-1,2-diphenyl-4-chloro-but-1-ene.

9. A compound according to claim 6, which is

N-[4-(4-chloro-1,2-diphenylbut-1-enyl)phenyl]-N',N'-dimethylethane-1,2-diamine.

10. A triphenylethylene according to claim 1, wherein R1 and R2, which are the same or different are

a) H, halogen, OCH_3, OH; or

b) $-Y-(CH_2)_nCH_2-O-R6$

where Y is O, NH or S and n is an integer from 1 to 4; and R6 is H, $-CH_2CH_2OH$, or $-CH_2CH_2Cl$.

11. A triphenylethylene according to claim 10 where Y is O.

12. A triphenylethylene according to claim 10 where Y is S.

13. A triphenylethylene according to claim 10 where Y is NH.

14. A compound according to claim 11, which is selected from the group consisting of

2-{4-[4-chloro-2-phenyl-1-(4-fluorophenyl)but-1-enyl]phenoxy}ethanol,
2-{4-[4-chloro-2-phenyl-1-(4-chlorophenyl)but-1-enyl]phenoxy}ethanol,
3-{4-chloro-1-[4-(2-hydroxyethoxy)phenyl]-2-phenyl-but-1-enyl}-phenol,
4-{1-(2-chloroethyl)-2-[4-(2-hydroxyethoxy)phenyl]-2-phenylvinyl}phenol,
2-{4-[4-chloro-1,2-bis(4-chlorophenyl)but-1-enyl]phenoxy}ethanol,
2-{4-[4-chloro-2-(4-chlorophenyl)-1-(4-methoxyphenyl)but-1-enyl]phenoxy}ethanol,

2-(4-{4-chloro-1-[4-(2-hydroxyethoxy)phenyl]-2-phenyl-but-1-enyl}-phenoxy)-1-ethanol,

2-[3-(4-chloro-1,2-diphenyl-but-1-enyl)phenoxy]ethanol,
3-[4-(4-chloro-1,2-diphenylbut-1-enyl)phenoxy]propan-1-ol,
2-{2-[4-(4-chloro-1,2-diphenylbut-1-enyl)phenoxy]ethoxy}ethanol,
3-[4-(4-chloro-1,2-diphenylbut-1-enyl)phenoxymethyl]pentan-3-ol,
1-(4-{2-[(2-chloroethoxy]ethoxy}phenyl)-4-chloro-1-(4-chlorophenyl)-2-phenyl-but-1-ene and

1-(4-{2-[(2-chloroethoxy]ethoxy}phenyl)-4-chloro-1-(4-fluorophenyl)-2-phenyl-but-1-ene.

15. A compound according to claim 12, which is

2-[4-(4-chloro-1,2-diphenyl-but-1-enyl)-phenylsulfanyl]ethanol.

16. A compound according to claim 13, which is

2-[4-(4-chloro-1,2-diphenyl-but-1-enyl)phenylamino]ethanol.

17. A compound according to claim 1, which is selected from the group consisting of

3-[4-(4-chloro-1,2-diphenylbut-1-enyl)phenoxymethyl]pentan-3-ol,
2-[4-(4-chloro-1,2-diphenylbut-1-enyl)phenoxy]butan-1-ol,
3-[4-(4-chloro-1,2-diphenyl-but-1-enyl)phenoxy]propane-1,2-diol,
3-{4-[4-chloro-1-(4-chlorophenyl)-2-phenyl-but-1-enyl]phenoxy}propane 1,2 diol,

4-chloro-1-[4-(2-methylsulfanyl-ethoxy)phenyl]-1,2-diphenyl-but-1-ene,
4-chloro-1-[4-(2-chloroethoxy)phenyl]-1,2-bis(4-chlorophenyl)-but-1-ene,

and

{4-[4-chloro-1-(4-chlorophenyl)-2-phenylbut-1-enyl]phenoxy}acetic acid.

18. A pharmaceutical composition comprising an amount effective to produce a tissue specific estrogen and/or antiestrogenic effect of said novel selective estrogen receptor modulator compound according to claim 1 or non-toxic pharmaceutically acceptable salt thereof, and a pharmaceutically compatible acceptable carrier therefor.

19. A method of producing a tissue specific estrogenic and/or antiestrogenic effect in a subject in which such an effect is desired which comprises administering to said subject said novel selective estrogen receptor modulator compound according to claim 1, or a non-toxic pharmaceutically acceptable salt thereof in an amount sufficient to produce the desired effect.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/FI 00/00946

A. CLASSIFICATION OF SUBJECT MATTER

IPC7: C07C 43/23, C07C 217/18, A61K 31/085, A61K 31/135, A61P 5/32, A61P 5/30, A61P 15/12, A61P 19/10

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7: C07C

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0095875 A2 (FARMOS GROUP LTD.), 7 December 1983 (07.12.83)	1-19
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X	WO 9607402 A1 (ORIONYHTYMÄ OY), 14 March 1996 (14.03.96)	1-19
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X	WO 9635417 A1 (CANCER RESEARCH CAMPAIGN TECHNOLOGY LIMITED), 14 November 1996 (14.11.96), page 4, line 14 - page 8, line 3	1-19
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X	WO 9732574 A1 (ORIONYHTYMÄ OY), 12 Sept 1997 (12.09.97)	1-19
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[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
1 February 2001	08 -02- 2001
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer Gerd Strandell/EÖ Telephone No. +46 8 782 25 00

Form PCT/ISA/210 (second sheet) (July 1998)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/FI 00/00946

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 9942427 A1 (ORION CORPORATION), 26 August 1999 (26.08.99)	1-19
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X	J. steroid Biochem., Volume 36, No 3, 1990, Niklas H. Simberg et al, "In vitro and in vivo binding of toremifene and its metabolites in rat uterus" page 197 - page 202	1-19
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P,X	WO 9963974 A2 (ENDORECHERCHE, INC.), 16 December 1999 (16.12.99), claims 9,13,16,17	1-19
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P,X	Human Reproduction Update, Volume 6, No 3, May 2000, Steven R. Goldstein et al, "A pharmacological review of selective oestrogen receptor modulators" page 212 - page 224	1-19
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P,X	J Soc Gynecol Investig, Volume 7, No 1, 2000, Leo Plouffe, "Selective Estrogen Receptor Modulators (SERMs) in Clinical Practice", page S38 - page S46	1-19
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P,X	Endocrinology, Volume 141, No 2, February 2000, Qiang Qu et al, "Selective Estrogenic Effects of a Novel Triphenylethylene Compound, FC1271a, on Bone, Cholesterol Level, and Reproductive Tissues in Intact and Ovariectomized Rats" page 809 - page 820	1-19
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INTERNATIONAL SEARCH REPORT

International application No.
PCT/FI00/00946

Box I **Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)**

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 19
because they relate to subject matter not required to be searched by this Authority, namely:

see next sheet

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II **Observations where unity of invention is lacking (Continuation of item 2 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

International application No.
PCT/FI00/00946

Claim 19 relates to a method of treatment of the human or animal body by surgery or by therapy/a diagnostic method practised on the human or animal body/Rule 39.1(iv). Nevertheless, a search has been executed for this claim. The search has been based on the alleged effects of the compound/composition.

INTERNATIONAL SEARCH REPORT
Information on patent family members

27/12/00

International application No.
PCT/FI 00/00946

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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		AT 192983 A	15/11/86
		AT 383344 B	25/06/87
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INTERNATIONAL SEARCH REPORT
Information on patent family members

27/12/00

International application No.
PCT/FI 00/00946

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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